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RESPIRATORY CARE

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SPECIAL ISSUE
RESPIRATORY CARE OF INFANTS
AND CHILDREN
Part I

- Implications for Adult Care Practitioners
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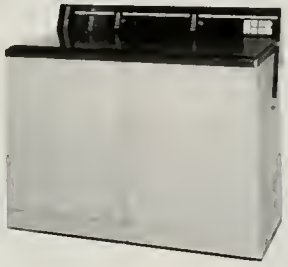

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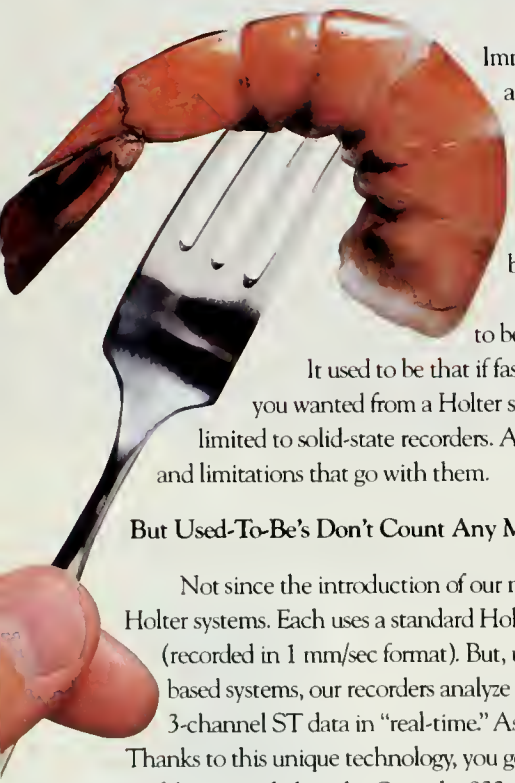

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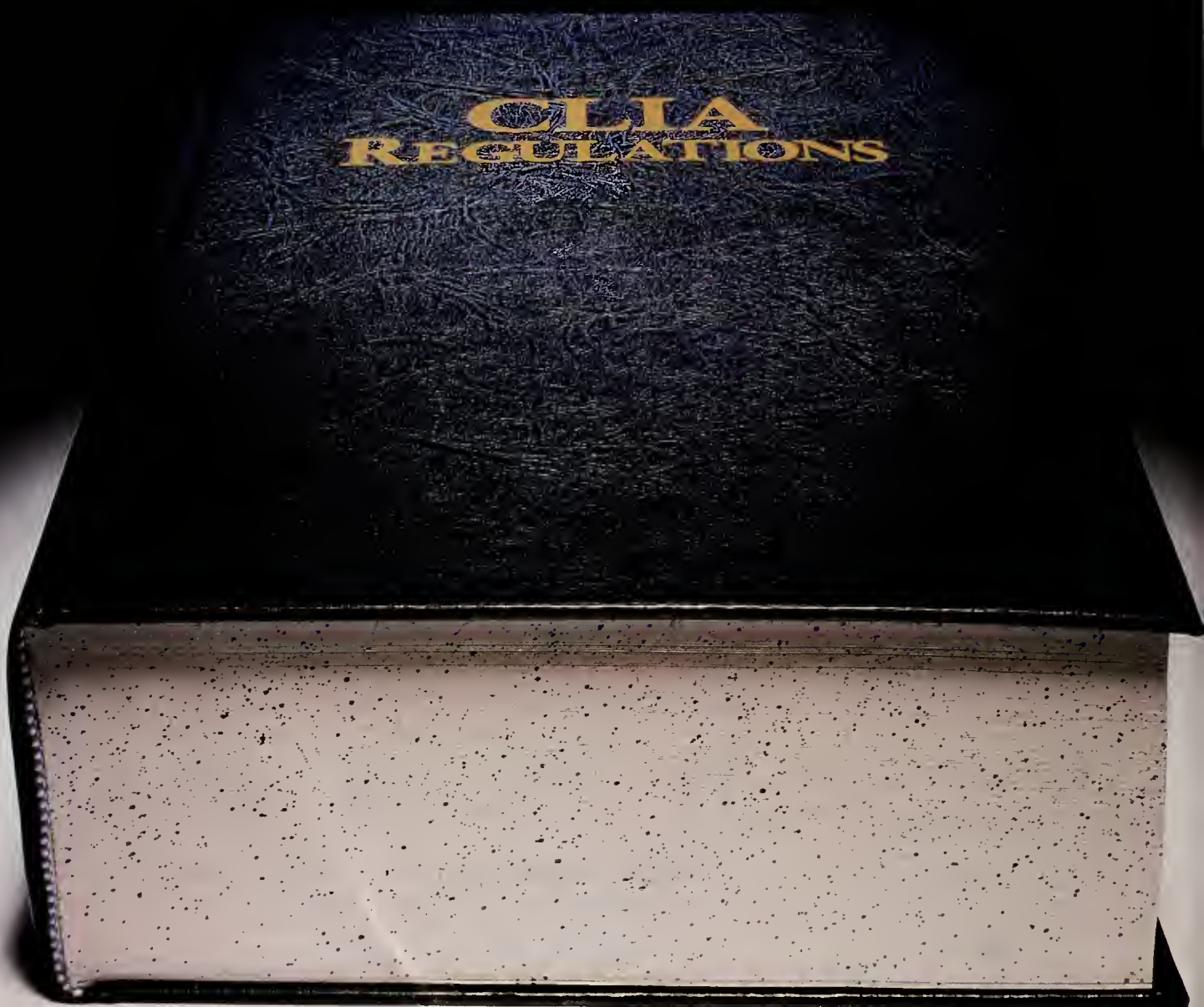

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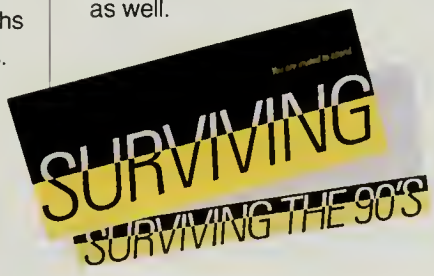

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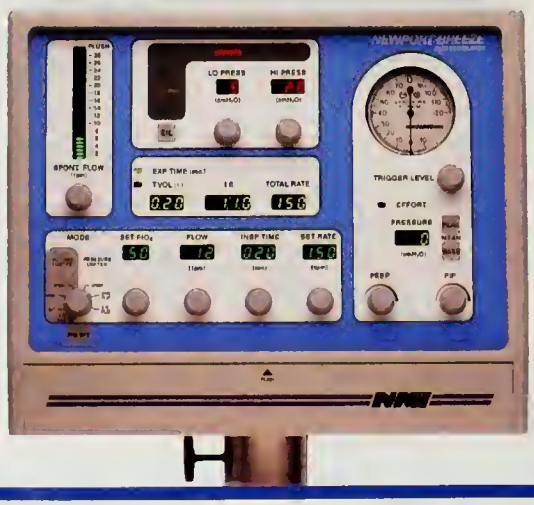

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Reviews, Editorials, and Statements To Note

Sudden Infant Death Syndrome and Small Airway Occlusion: Facts and a Hypothesis (review)—FD Martinez. Pediatrics 1991;87:190.

Pulmonary Function as a Phenotype Physiologic Marker of Cardiovascular Morbidity and Mortality (editorial)—ST Weiss. Chest 1991;99:265. (Pertains to Higgins et al paper abstracted below.)

Guidelines for Standards of Care for Patients with Acute Respiratory Failure on Mechanical Ventilatory Support (special article).—Task Force on Guidelines, Society of Critical Care Medicine. Crit Care Med 1991;19:275.

Pulmonary Function and Cardiovascular Risk Factor Relationships in Black and in White Young Men and Women:The CARDIA Study—M Higgins, JB Keller, LE Wagenknecht, MC Townsend, et al. Chest 1991;99:315.

Pulmonary function is known to be related inversely to incidence of coronary heart disease, congestive heart failure, chronic obstructive lung disease, lung cancer, and death from all causes. Reasons for some of these associations are poorly understood. Relationships between cardiovascular disease risk factors and pulmonary function were examined in 5,115 18- to 30-year-old black and white male and female participants in the study of Coronary Artery Risk Development in Young Adults (CARDIA). Forced expiratory volume in 1 s adjusted for height (FEV_1/Ht^2) was significantly lower in smokers than nonsmokers and in persons who reported shortness of breath; FEV_1/Ht^2 was correlated positively with a history of strenuous physical activity, duration of exercise on the treadmill, and high-density lipoprotein cholesterol. It was associated negatively with skinfold thicknesses, serum triglycerides, fasting serum insulin, and the Cook Medley scale of hostility. The association between pulmonary function and heart disease risk may reflect associations with physical fitness, vigor, fatness, and lipid profiles, as well as with cigarette smoking.

Delivery of Aerosolized Medication to Intubated Babies—KL Watterberg, AR Clark, HW Kelly, S Murphy. Pediatr Pulmonol 1991; 10:136.

We studied the delivery of aerosolized cromolyn sodium to intubated babies, and evaluated the effect of changes in delivery techniques. In addition, we compared these results with an in vitro model of aerosol delivery. Cromolyn sodium was used as a marker because once the drug is absorbed, it is excreted unchanged, approximately 50% in urine and 50% in bile. We demonstrated that, in vitro, a conventional, jet-type nebulizer aerosolized 20.5% of a test dose of cromolyn, and only 5.5% of the dose was recovered after passage through 60 cm of ventilator tubing and an endotracheal tube adapter. This increased to 44.5% nebulized and 19% recovered when the volume nebulized was increased from 2 mL to 5 mL. A submicronic nebulizer aerosolized 40% and delivered 33.5% of the test dose. A 20 mg dose of nebulized cromolyn sodium was used as a test dose in infants, after which urine was collected for 4 hours. Forty-three urine samples were collected, after the delivery of cromolyn test doses, from nine babies (16-128 days old) intubated for bronchopulmonary dysplasia. Both the jet and submicronic nebulizers were tested in two positions: (1) in place of the ventilator humidifier, and (2) at the endotracheal tube adapter. There were no statistically significant differences in cromolyn delivery for any system configuration. In all situations, means of less than 0.1% of the test dose were recovered in the urine. We estimated that in all cases, $< 1\%$ of the test dose (approximately 50-100 μg of cromolyn) had been deposited in the lung. These results show that,

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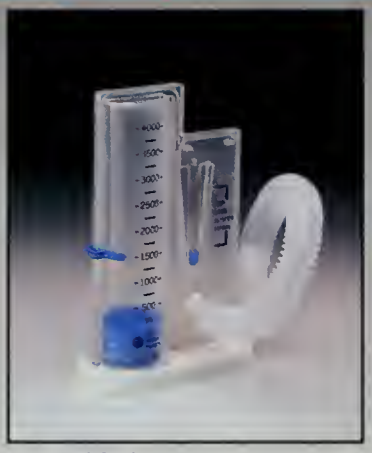

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although the submicronic nebulizer aerosolized cromolyn more efficiently, no additional cromolyn could be detected in infants. We speculate that a significant portion of the smaller particles are exhaled.

Morphometric Analysis of the Lung in Bronchopulmonary Dysplasia—LR Margraf, JF Tomashefski, MC Bruce, BB Dahms. Am Rev Respir Dis 1991;143:391.

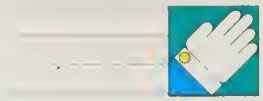
We studied lung development in children with or without bronchopulmonary dysplasia (BPD) using light microscopic morphometry and thick lung sections stained for elastic fibers. One lung was obtained at autopsy from each of eight patients with BPD (ages 2 to 28 months) and six children (ages 5 days to 51 months) who died without lung disease. Patients with BPD demonstrated severe somatic growth retardation and had reduced lung volumes with abnormal lobar volume proportions. In the central bronchi mean volume proportion of glands and smooth muscle was increased in BPD. Bronchiolar density was also increased, but it tended to normalize with advancing age. Mean bronchiolar diameter was slightly smaller in BPD, and bronchiolar smooth muscle hypertrophy was a constant histologic feature. The most striking change, however, was noted in alveolar structure and development. Total alveolar number was severely decreased in patients with BPD compared with that in control subjects, and there was little evidence of compensatory alveolar development with increasing age. Lung internal surface area was correspondingly reduced, and mean linear intercept was increased. Sections stained for elastic tissue demonstrated in the patients with BPD a simplified acinar structure with thickened, tortuous, and irregularly distributed alveolar elastic fibers. We conclude that in severe, fatal BPD there is marked impairment of lung development with alveolar hypoplasia and reduced internal surface area. In addition, bronchial and bronchiolar smooth muscle hypertrophy and bronchial gland hyperplasia may be important contributing factors to airflow limitation.

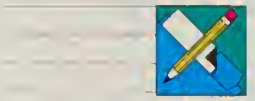
Upper Respiratory Tract Infections in Young Children: Duration of and Frequency of Complications—ER Wald, N Guerra, C Byers. Pediatrics 1991;87:129.

This study was performed to determine the usual duration of community-acquired viral upper respiratory tract infections and the incidence of complications (otitis media/sinusitis) of these respiratory tract infections in infancy and early childhood. Children in various forms of child-care arrangements (home care, group care, and day care) were enrolled at birth and observed for 3 years. Families were telephoned every 2 weeks to record on a standardized form the type and severity of illnesses experienced during the previous interval. Only children remaining in their original child-care group for the entire study period were compared. The mean duration of an upper respiratory tract infection varied between 6.6 days (for 1- to 2-year-old children in home care) and 8.9 days (for children younger than 1 year in day care). The percentage of apparently simple upper respiratory tract infections that lasted more than 15 days ranged from 6.5% (for 1- to 3-year-old children in home care) to 13.1% (for 2- to 3-year-old children in day care). Children in day care were more likely than children in home care to have protracted respiratory symptoms. Of 2,741 respiratory tract infections recorded for the 3-year period, 801 (29.2%) were complicated by otitis media. During the first 2 years of life, children in any type of day care were more likely than children in home care to have otitis media as a complication of upper respiratory tract infection. In Year 3, the risk of otitis media was similar in all types of child care.

Pulse Oximetry versus Measured Arterial Oxygen Saturation: A Comparison of the Nellcor N100 and the Biox III—P Lebecque, P Shango, M Stijns, A Vliers, AL Coates. Pediatr Pulmonol 1991; 10:132.

Pulse oximetry is noninvasive, fast, and simple, making it a very popular way of assessing oxygenation in pediatric patients. However, there are few studies that establish the accuracy of this technology over a wide range of oxygen saturations in children. This study, done in 47 children aged from 1 day to 16 years with congenital heart disease and undergoing cardiac catheterization, compared the direct measurement of arterial oxygen saturation to values from pulse oximetry. Oxygen saturation was measured by an IL-282 CO-Oximeter, which also measured carboxyhemoglobin and methemoglobin, and was compared to values obtained from both a Biox III and Nellcor N100. Both pulse oximeters gave values that closely correlated with the actual saturation ($r = 0.91$ and 0.93, respectively) with standard errors of the estimate of 4.1 and 3.2%, respectively. For both devices, the error increased with decreasing saturations, being progressively larger below a saturation of 80%. The difference between the actual saturation and that measured by pulse oximetry bore no relationship to the presence of carboxyhemoglobin, methemoglobin, fetal hemoglobin, bilirubin, cardiac index, or age of the patient. In conclusion, pulse oximetry, while a very useful technology in pediatrics, must be interpreted with some caution in children with severe cyanosis.





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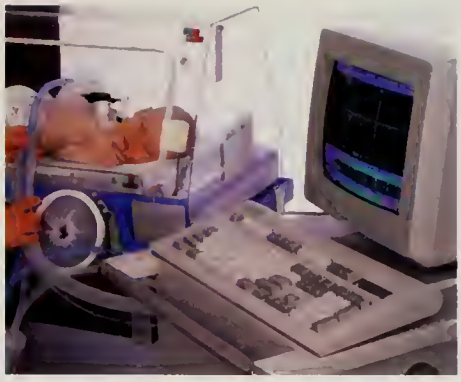

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Should You Cancel the Operation When a Child Has an Upper Respiratory Tract Infection?—MM Cohen, CB Cameron. Anesth Analg 1991;72:282.

Cancelling an operation when a child has an upper respiratory tract infection (URI) is not always feasible or practical. Yet we know very little about the additional risk posed by a URI occurring in a child undergoing anesthesia and surgery. Using a large prospectively collected pediatric anesthesia database, we studied 1,283 children with a preoperative URI and 20,876 children without a URI. We found that children with a URI were two to seven times more likely to experience respiratory-related adverse events during the intraoperative, recovery room, and postoperative phases of their operative experience. Although these children also experienced significant disruptions in temperature regulation, they were not at risk for any other deleterious events. The elevation in risk after URI as compared with children without a URI was not explained by differences in age, physical status scores, surgical site, and emergency or elective status. However, if a child had a URI and had endotracheal anesthesia, the risk of a respiratory complication increased 11-fold (95% confidence intervals 6.8, 18.1). We conclude that the administration of general anesthesia to children with a URI is not benign and that these children require more observation/management in all perioperative phases of their surgical procedure.

Bronchopulmonary Dysplasia: Improvement in Lung Function between 7 and 10 Years of Age—M Blayney, E Kerem, H Whyte, H O'Brodovich. J Pediatr 1991; 118:201.

To evaluate the natural history of bronchopulmonary dysplasia, we studied the same 32 patients at a mean age of 7 and 10 years. The group as a whole had normal height and weight percentiles, and each child grew along his or her established somatic growth curve. Although some children had abnormal values, the group maintained a normal mean total lung capacity and functional residual capacity. The mean residual volume and the residual volume/total lung capacity ratios were elevated at both ages. At age 7 years the 19 patients (59%) who had a forced expiratory volume in 1 second (FEV_1) of $< 80\%$ had "catch up" improvement by 10 years of age ($65 \pm 11\%$ to $72 \pm 16\%$ of predicted value; $p < 0.05$). All the children who had a normal FEV_1 at 7 years of age continued to have a normal FEV_1 at age 10 years. Resting single-breath carbon monoxide uptake by the lung was normal when measured at age 10 years. The majority of patients had a positive methacholine challenge test result at both ages, although there was a low incidence of clinically diagnosed asthma. This study demonstrates that patients with bronchopulmonary dysplasia who have normal lung function at age 7 have had normal lung growth and that those with evidence of mild to moderate lung disease have continued lung growth or repair, or both, during their school years.

Measurement of Respiratory System Resistance by Forced Oscillation in Normal Children: A Comparison with Spirometric Values—P Lebecque, K Desmond, Y Swartebroeckx, P Dubois, J Lulling, A Coates. Pediatr Pulmonol 1991; 10:117.

In 377 children, the commercially available Siregnost FD-5 was used to measure respiratory system resistance (Rrs) by forced oscillation at 10 Hz. The children were between 3 and 18 years of age and, by a detailed questionnaire and conventional pulmonary function testing in 335, they were shown to be representative of the normal pediatric population. There was a linear relationship between Rrs and height ($Rrs = 13.9–0.064 \times ht(cm)$, $r = –0.87$). Children less than 6 years of age had no trouble with using the forced oscillation technique. The smoking of tobacco in the house, the presence of carpets in the child's bedroom, or an atopic family history, alone or in combination, had no influence on Rrs or on any spirometric measure. Forced oscillation is useful in children too young to be able to cooperate with conventional pulmonary function testing.

Closure of the Ductus Arteriosus with Indomethacin in Ventilated Neonates with Respiratory Distress Syndrome: Effects on Pulmonary Compliance and Ventilation—JL Stefano, S Abbasi, SA Pearlman, ML Spear, KL Esterly, VK Bhutani. Am Rev Respir Dis 1991;143:236.

The reported effects of indomethacin on pulmonary compliance are variable depending upon the patient population and on the degree to which indomethacin resulted in successful ductal closure. Eleven fluid-restricted, furosemide-treated premature infants being mechanically ventilated for respiratory distress syndrome (RDS) who also had a significant patent ductus arteriosus (PDA) had pulmonary function testing performed before and after successful closure of the PDA. The diagnosis of a significant PDA was made by clinical and echocardiographic criteria. Indomethacin was administered at a dosage of 0.2 $mg \cdot kg \cdot dose^{-1}$ every 12 to 18 h for 1 to 3 doses. To control for the 48-h time interval to achieve ductal closure, nine premature infants being ventilated for RDS but who did not have a significant PDA also had pulmonary function evaluations performed before and after the 48 h. Also, to control for the independent effect

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† Shapiro S, Hendler J, Ogirala R, Aldrich T, Shapiro MB: An evaluation of the accuracy of Assess and Mini-Wright peak flow meters. *Chest 99*:358-362, 1991.

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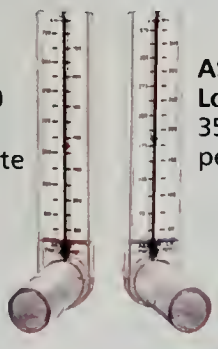

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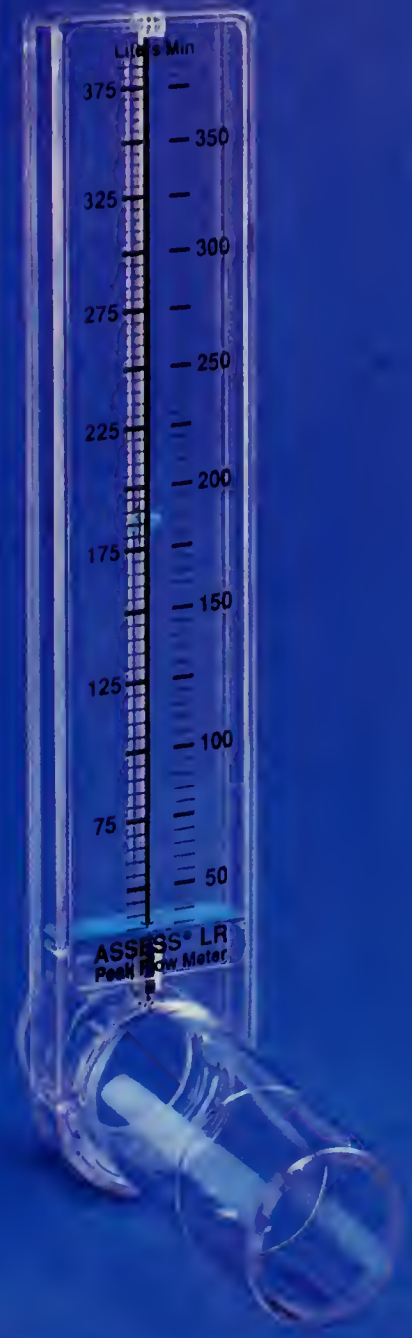

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of fluid restriction and diuretic therapy on pulmonary compliance, eight such premature infants with a PDA had pulmonary function evaluations performed at a 48-h interval. Successful closure of the ductus with indomethacin was associated with an improvement in compliance and ventilation parameters in all infants in the indomethacin-treated infants. In the indomethacin-treated group, the mean percent improvements were noted in the following parameters: CL_{dyn}, 59.2%; CL_I, 78.3%; CL_E, 63.3%; V_T, 63.3%; $\dot{V}_E$, 54.6%. There were no significant changes in the pulmonary functions in the 48-h RDS or the 48-h PDA fluid-restricted, furosemide-treated control groups. In conclusion, successful closure of the ductus with indomethacin causes a significant improvement in compliance and ventilation parameters in infants being mechanically ventilated for RDS.

Reliability of the Bronchoscopic Protected Catheter Brush in the Diagnosis of Pneumonia in Mechanically Ventilated Patients—FR De Castro, JS Violan, BL Capuz, JC Luna, BG Rodriguez, JLM Alonso. Crit Care Med 1991;19:171.

OBJECTIVE: To assess the usefulness of the telescoping plugged catheter in the diagnosis of nosocomial pneumonia. DESIGN: Prospective study. PATIENTS: A total of 103 ventilated patients with suspected pneumonia were prospectively studied over 20 months. RESULTS: The quantitative cultures of the protected brush specimen detected pulmonary bacterial infection ($\geq 10^3$ cfu/mL) in 49 (47.5%) patients. Subsequent follow-up confirmed pneumonia in 41 patients; in only one patient was a positive protected brush specimen culture established as a false-positive result. There were 54 patients with $< 10^3$ cfu/mL and the diagnosis was excluded in 36 of them. We identified eight patients with false-negative protected brush specimen cultures. The results obtained by this technique allowed us to modify treatment in 49 (47.5%) patients. CONCLUSIONS: The telescoping plugged catheter demonstrated significant bacterial infection in a relatively small proportion of patients in whom bacterial lung infection was suspected. This technique can be safely performed and is a sensitive and specific method to establish the cause of pneumonia, thus allowing specific treatment and the avoidance of inappropriate antibiotic therapy.

Sleep Apnea and Hypoxemia in Recently Weaned Premature Infants with and without Bronchopulmonary Dysplasia—KC Sekar, JC Duke. Pediatr Pulmonol 1991; 10:112.

Infants with bronchopulmonary dysplasia (BPD) experience significant hypoxemia. Apnea indices and oxygen saturation levels of ten infants with BPD were compared to ten healthy premature infants who were evaluated to rule out apnea or bradycardia prior to discharge from the hospital. Infants with BPD who had been recently (< 7 days) weaned from supplemental oxygen were evaluated on and off supplemental oxygen. Premature controls had never received oxygen nor ventilation assistance. Infants with BPD were born significantly more prematurely (28.1 ± 1.0 vs 33.0 ± 3.9 weeks; $p = 0.0012$) while chronologic ages at the time of evaluation, adjusted for prematurity, were equal (37.1 ± 3.1 vs 38.0 ± 2.7 weeks). Comparisons of apnea densities (expressed as percent of sleep time) between BPD and non-BPD prematures revealed the following: neither the average obstructive apnea (0.15 ± 0.36 vs 0.14 ± 0.31) nor periodic breathing densities (6.0 ± 8.56 vs 10.2 ± 5.84) were different. Infants with BPD experienced significantly more central apnea (0.62 ± 0.34 vs 0.16 ± 0.11; $p = 0.003$) than did non-BPD prematures. Average oxygen saturation levels were significantly less among BPD vs non-BPD prematures ($90.0 \pm 10.18\%$ vs $95.7 \pm 4.33\%$; $p = 0.033$). When supplemented with oxygen, BPD prematures had significantly higher saturation ($\bar{x} = 94.5\%$) than when breathing room air ($\bar{x} = 90.0\%$). Both central apnea and periodic breathing densities declined significantly with this improvement in saturation (0.64 vs 0.04% and 6.0 vs 1.4%, respectively). These data suggest that saturation status may indicate central respiratory stability in chronic lung disease.

Influence of Noninvasive Positive Pressure Ventilation on Inspiratory Muscles—RS Goldstein, JA De Rosie, MA Avendano, TE Dolmage. Chest 1991;99:408.

Intermittent positive pressure ventilation reduces inspiratory muscle electromyographic activity among patients with restrictive ventilatory failure. It has therefore been suggested that the reduction of energy expenditure at night could result in improved inspiratory muscle function during the day. Reported successes with nocturnal ventilation have not included measurements of inspiratory muscle endurance. We therefore electively ventilated six (five female, one male) patients (mean ± SD) aged 36 ± 13 years in whom respiratory failure (room air P_{aCO_2}, 60 ± 13 torr; P_{aO_2}, 44 ± 11 torr; S_{aO_2}, $75 \pm 12\%$) was consequent on restrictive ventilatory disease (vital capacity, $25 \pm 7\%$ predicted; FEV_1/FVC, $81 \pm 12\%$; total lung capacity, $40 \pm 5\%$ predicted; $MIP_{RV} -42 \pm 10$ cm H_2O; MEP, 81 ± 28 cm H_2O). Positive pressure ventilation was administered with a customized closely fitting nasal mask attached to a volume-cycled pressure-limited ventilator. Full respiratory polysom-

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Dramatic reductions in neonatal morbidity and mortality reported in clinical trials[1-5]

Improvement in clinical outcome after EXOSURF Neonatal has been significant in infants at risk of developing RDS as well as those with established RDS. Prophylactic as well as rescue treatment with EXOSURF Neonatal has dramatically reduced morbidity and mortality in infants weighing greater than 700 grams.

SIGNIFICANT REDUCTIONS IN OVERALL MORTALITY FROM ANY CAUSE IN MIDDLE-SIZE AND LARGE INFANTS[2-5]
(Percent reductions with EXOSURF)

	Prophylactic treatment		Rescue treatment	
Age	*Single Dose*[2] 700-1100 grams (N=446)	*One vs Three Doses*[3] 700-1100 grams (N=716)	*Two Dose*[4] 700-1350 grams (N=419)	*Two Dose*[5] 1250 grams and above (N=1232)
≤10 Days	—	—	59%§	35%
≤28 Days	40%*	44%†	52%§	39%
≤1 Year	44%†	41%‡	46%§	31%

*P=0.022. †P=0.002. ‡P<0.05. §P<0.001. ‖P=0.039. N=Number of infants enrolled in the clinical trials.

A single prophylactic dose of EXOSURF Neonatal reduced 1-year mortality by 44%. Two additional prophylactic doses provided an additional 41% reduction in 1-year mortality.[3]

SIGNIFICANT REDUCTIONS IN MORTALITY FROM RDS IN MIDDLE-SIZE AND LARGE INFANTS[2,4,5]
(Percent reductions with EXOSURF)

	Prophylactic treatment	Rescue treatment	
	Single Dose[2] 700-1100 grams (N=446)	*Two Dose*[4] 700-1350 grams (N=419)	*Two Dose*[5] 1250 grams and above (N=1232)
Reduction in death from RDS	58%*	66%†	63%†

*P=0.011. †P=0.007. ‡P=0.009 N=Number of infants enrolled in the clinical trials.

SIGNIFICANT REDUCTION IN CARDIOPULMONARY DESTRUCTION TO DAY 28 FOLLOWING TWO-DOSE RESCUE TREATMENT[4,5]

(Percent reductions with EXOSURF)

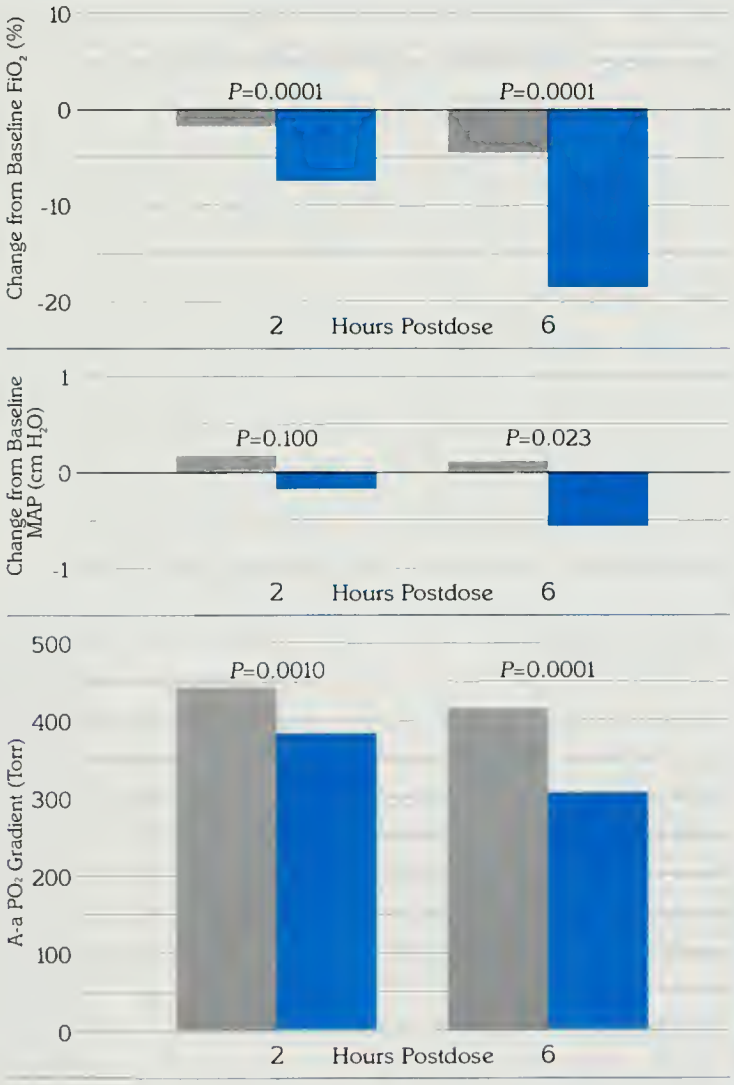
Birth weight	Reduction in death at 28 days or survival with broncho-pulmonary dysplasia (BPD)
700-1350[4] (N=419)	34%*
1250 and above[5] (N=1232)	43%*

*P=0.002. N=Number of infants enrolled in the clinical trials.

Rapid onset of action documented in rescue use[4]

Improvements in mean FiO_2 and mean alveolar-arterial PO_2 (A-a) gradient were present by 2 hours after dosing in middle-size babies (700-1350 grams). Improvements in mean airway pressures began sometime between 2 and 6 hours in middle-size babies. These improvements persisted for at least 7 days.

SIGNIFICANT IMPROVEMENTS IN SUPPLEMENTAL OXYGEN NEEDS AND VENTILATORY REQUIREMENTS SEEN IN MIDDLE-SIZE BABIES[4]



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Efficacy and impressive safety profile of EXOSURF® Neonatal™ confirmed in continued widespread use[6]

In North American controlled clinical trials, more than 2600 premature infants received EXOSURF Neonatal. Under the year-long Treatment IND, over 11,400 infants received EXOSURF Neonatal. In the six months following its release for marketing, EXOSURF Neonatal has been given to 10,000 infants in more than 750 hospitals.

There are no known infectious or immunologic risks associated with EXOSURF Neonatal use. In controlled clinical trials, adverse events were comparable to those of placebo, with the exception of apnea and pulmonary bleeding. Infants receiving EXOSURF Neonatal required less ventilatory support, possibly contributing to an increased incidence of apnea. Pulmonary bleeding occurred in 1% of control infants and 2% of treated infants in controlled trials. In the treatment IND, pulmonary bleeding was reported in 4% and mucous plugging at a rate of 3/1000. Pulmonary bleeding appears to be preventable with early diagnosis and appropriate treatment of patent ductus arteriosus.

One-year follow-up evaluated developmental outcomes[7]

Double-blind 1-year follow-up of more than 1450 infants enrolled in randomized trials showed that mental and motor scores appeared to be higher in tiny infants (<750 grams) as well as middle-size infants (750-1249 grams) who received Exosurf Neonatal.

Economic data analysis showed cost savings[8-10]

Three separate studies evaluated the economic impact of a single prophylactic dose of EXOSURF Neonatal, two-dose rescue treatment in 700- to 1350-gram infants, and two-dose rescue treatment during the neonatal period in infants weighing over 1350 grams. Results indicate that both prophylactic treatment and rescue treatment are cost-effective. Mean hospital charges were $6451 less for large infants receiving two-dose rescue treatment versus air in the first 28 days of life.[10]

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- **Easy on infant** To assist the distribution of EXOSURF Neonatal in the lungs, the infant is simply turned from midline position to the right after the first half-dose, and from midline position to the left after the second half-dose.

References: 1. Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. *J Pediatr.* 1990;117:947-953. **2.** Corbet A, Bucciarelli R, Goldman S, et al. Decreased mortality in small premature infants treated at birth with a single dose of synthetic surfactant: a multi-center controlled trial. *J Pediatr.* 1991;118:277-284. **3.** Gerdes J, Cook L, Beaumont E, Corbet A, Long W American EXOSURF Pediatric Groups I and II. Effects of three vs. one prophylactic doses of EXOSURF Neonatal in 700- to 1100-gram neonates. *Pediatr Res.* 1991;29(no. 4, pt 2):214A. Abstract. **4.** Long W, Thompson T, Sundell H, et al. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. *J Pediatr.* 1991;118:595-605. **5.** U.S. and Canadian EXOSURF Pediatric Study Groups Effects of two rescue doses of EXOSURF® Pediatric in 1232 infants ≥1250 grams. *Pediatr Res.* 1990;27(no. 4, pt 2):320A. Abstract **6.** Data on file, Burroughs Wellcome Co.,1991. **7.** Walter D, McGuinness G, Bose C, et al Double-blind one-year follow-up in 1450 infants randomized to EXOSURF® Neonatal or air. *Pediatr Res.* 1991;29(no. 4, pt 2):270A. Abstract. **8.** Sell M, Corbet A, Gong A, et al Economic impact of a single prophylactic dose of EXOSURF® Neonatal in 700- to 1100-gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):265A. Abstract. **9.** Mammel M, Mullett M, Derleth D, et al Economic impact of two rescue doses of EXOSURF® Neonatal in 700-1350 gram infants. *Pediatr Res.* 1991,29(no 4, pt 2):260A. Abstract. **10.** Schumacher R, Burchfield D, Vaughan R, et al Economic impact of two rescue doses of EXOSURF® Neonatal in ≥1350 gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):264A. Abstract

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INDICATIONS AND USAGE: Exosurf Neonatal is indicated for

1 **Prophylactic** treatment of infants with birth weights of less than 1350 grams who are at risk of developing ROS (see PRECAUTIONS),

2 **Prophylactic** treatment of infants with birth weights greater than 1350 grams who have evidence of pulmonary immaturity and

3 **Rescue** treatment of infants who have developed RDS.

CONTRAINDICATIONS: There are no known contraindications to treatment with Exosurf Neonatal

WARNINGS: **Intratracheal Administration Only**: Exosurf Neonatal should be administered only by instillation into the trachea. **General**: The use of Exosurf Neonatal requires expert clinical care by experienced neonatologists and other clinicians who are accomplished at neonatal intubation and ventilatory management. Adequate personnel, facilities, equipment, and medications are required to optimize perinatal outcome in premature infants. Instillation of Exosurf Neonatal should be performed **only** by trained medical personnel experienced in airway and clinical management of unstable premature infants. Vigilant clinical attention should be given to all infants prior to, during, and after administration of Exosurf Neonatal. **Acute Effects**: Exosurf Neonatal can rapidly affect oxygenation and lung compliance. **Lung Compliance**. If chest expansion improves substantially after dosing, peak ventilator inspiratory pressures should be reduced immediately, without waiting for confirmation of respiratory improvement by blood gas assessment. Failure to reduce inspiratory ventilator pressures rapidly in such instances can result in lung overdistention and fatal pulmonary air leak. **Hyperoxia**: If the infant becomes pink and transcutaneous oxygen saturation is in excess of 95%, FiO_2 should be reduced in small but repeated steps (until saturation is 90 to 95%) without waiting for confirmation of elevated arterial pO_2 by blood gas assessment. Failure to reduce FiO_2 in such instances can result in hyperoxia. **Hypocarbia**. If arterial or transcutaneous CO_2 measurements are <30 torr, the ventilator rate should be reduced at once. Failure to reduce ventilator rates in such instances can result in marked hypocarbia, which is known to reduce brain blood flow. **Pulmonary Hemorrhage**: In the single study conducted in infants weighing <700 grams at birth, the incidence of pulmonary hemorrhage (10% vs 2% in the placebo group) was significantly increased in the Exosurf Neonatal group. None of the five studies involving infants with birth weights >700 grams showed a significant increase in pulmonary hemorrhage in the Exosurf Neonatal group. In a cross-study analysis of these five studies, pulmonary hemorrhage was reported for 1% (14/1420) of infants in the placebo group and 2% (27/1411) of infants in the Exosurf Neonatal group. Fatal pulmonary hemorrhage occurred in three infants, two in the Exosurf Neonatal group and one in the placebo group. Mortality from all causes among infants who developed pulmonary hemorrhage was 43% in the placebo group and 37% in the Exosurf Neonatal group. Pulmonary hemorrhage in both Exosurf Neonatal and placebo infants was more frequent in infants who were younger, smaller, male, or who had a patent ductus arteriosus. Pulmonary hemorrhage typically occurred in the first 2 days of life in both treatment groups. In more than 7700 infants in the open, uncontrolled study, pulmonary hemorrhage was reported in 4%, but fatal pulmonary hemorrhage was reported rarely (0.4%). In the controlled clinical studies, Exosurf Neonatal treated infants who received steroids more than 24 hours prior to delivery or indomethacin postnatally had a lower rate of pulmonary hemorrhage than other Exosurf Neonatal treated infants. Attention should be paid to early and aggressive diagnosis and treatment (unless contraindicated) of patent ductus arteriosus during the first 2 days of life (while the ductus arteriosus is often clinically silent). Other potentially protective measures include attempting to decrease FiO_2 preferentially over ventilator pressures during the first 24 to 48 hours after dosing, and attempting to decrease PEEP minimally for at least 48 hours after dosing. **Mucous Plugs**: Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the chance of mucous plugs obstructing the endotracheal tube. If endotracheal tube obstruction from such plugs is suspected, and suctioning is unsuccessful in removing the obstruction, the blocked endotracheal tube should be replaced immediately.

PRECAUTIONS:

General: In the controlled clinical studies, infants known prenatally or postnatally to have major congenital anomalies, or who were suspected of having congenital infection, were excluded from entry. However, these disorders cannot be recognized early in life in all cases, and a few infants with these conditions were entered. The benefits of Exosurf Neonatal in the affected infants who received drug appeared to be similar to the benefits observed in infants without anomalies or occult infection. **Prophylactic Treatment–Infants <700 Grams**: In infants weighing 500 to 700 grams, a single prophylactic dose of Exosurf Neonatal significantly improved FiO_2 and ventilator settings, reduced pneumothorax, and reduced death from RDS, but increased pulmonary hemorrhage (see WARNINGS). Overall mortality did not differ significantly between the placebo and Exosurf Neonatal groups (see Table 1 in full product information). Data on multiple doses in infants in this weight class are not yet available. Accordingly, clinicians should carefully evaluate the potential risks and benefits of Exosurf Neonatal administration in these infants. **Rescue Treatment–Number of Doses**: A small number of infants with ROS have received more than two doses of Exosurf Neonatal as rescue treatment. Definitive data on the safety and efficacy of these additional doses are not available. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Exosurf Neonatal at concentrations up to 10,000 µg/plate was not mutagenic in the Ames Salmonella assay. Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Exosurf Neonatal. The effects of Exosurf Neonatal on fertility have not been studied.

ADVERSE REACTIONS:

General: Premature birth is associated with a high incidence of morbidity and mortality. Despite significant reductions in overall mortality associated with Exosurf Neonatal, some infants who received Exosurf Neonatal developed severe complications and either survived with permanent handicaps or died.

In controlled clinical studies evaluating the safety and efficacy of Exosurf Neonatal, numerous safety assessments were made. In infants receiving Exosurf Neonatal, pulmonary hemorrhage, apnea and use of methylxanthines were increased. A number of other adverse events were significantly reduced in the Exosurf Neonatal group, particularly various forms of pulmonary air leak and use of pancuronium. Tables 3 and 4 summarize the results of the major safety evaluations from the controlled clinical studies.

Table 3. Safety Assessments[a]—Prophylactic Treatment

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		1 vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo (Air) N=108	EXOSURF N=107	Placebo (Air) N=193	EXOSURF N=192	Placebo (Air) N=222	EXOSURF N=224	EXOSURF 1 Dose N=356	EXOSURF 3 Doses N=360
	% of Infants		% of Infants		% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)								
Overall	51	57	31	27	36	36	38	35
Severe IVH	26	25	10	8	13	14	9	9
Pulmonary Air Leak (PAL)								
Overall	52	48	16	11	32	25	29	27
Pneumothorax	23	10*	5	6	19	11*	14	12
Pneumopericardium	1	4	2	0	<1	1	1	1
Pneumomediastinum	2	1	2	3	7	1**	3	2
Pulmonary Interstitial Emphysema	43	44	13	7*	26	20	23	22
Death from PAL	4	6	<1	<1	2	1	2	1
Patent Ductus Arteriosus	49	53	66	70	50	55	59	57
Necrotizing Enterocolitis	2	4	11	13	3	4	6	2*
Pulmonary Hemorrhage	2	10**	2	4	1	4	4	6
Congenital Pneumonia	4	4	2	4	2	2	1	1
Nosocomial Pneumonia	10	10	2	4	4	7	14	15
Non-Pulmonary Infections	33	35	34	39	28	29	35	34
Sepsis	30	34	30	34	23	24	30	27
Death From Sepsis	4	4	3	3	1	2	3	2
Meningitis	4	6	3	1	2	3	1	2
Other Infections	7	4	5	3	6	10	10	11
Major Anomalies	3	1	2	4	7	4	4	4

Table 3. Safety Assessments[a]—Prophylactic Treatment (Cont.)

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		1 vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo (Air) N=108	EXOSURF N=107	Placebo (Air) N=193	EXOSURF N=192	Placebo (Air) N=222	EXOSURF N=224	EXOSURF 1 Dose N=356	EXOSURF 3 Doses N=360
	% of Infants		% of Infants		% of Infants		% of Infants	
Hypotension	70	77	52	47	59	62	54	50
Hyperbilirubinemia	22	21	63	61	27	31	20	21
Exchange Transfusion	4	3	1	2	2	2	3	1
Thrombocytopenia[b]	21	25	not available		9	8	12	10
Persistent Fetal Circulation	0	1	1	1	0	2*	1	<1
Seizures	11	8	2	2	11	9	6	5
Apnea	34	33	76	73	55	65*	62	68
Drug Therapy								
Antibiotics	96	99	98	96	98	99	>99	99
Diuretics	55	60	39	37	59	63	64	65
Anticonvulsants	14	18	23	24	20	16	9	8
Inotropes	46	40	20	20	26	20	28	27
Sedatives	62	71	65	64	63	57	52	52
Pancuronium	19	11	22	14*	19	13*	15	11
Methylxanthines	38	43	77	77	61	72*	75	82*

[a] All parameters were examined with "as-treated" analyses
[b] Thrombocytopenia requiring platelet transfusion
* p<0.05
** p<0.01

Table 4. Safety Assessments[a]—Rescue Treatment

Number of Doses / Birth Weight Range	Two Doses 700 to 1350 grams		Two Doses 1250 grams and above	
Treatment Group / Number of Infants	Placebo (Air) N=213	EXOSURF N=206	Placebo (Air) N=622	EXOSURF N=615
	% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)				
Overall	48	52	23	18*
Severe IVH	13	9	5	4
Pulmonary Air Leak (PAL)				
Overall	54	34***	30	18***
Pneumothorax	29	20*	20	10***
Pneumopericardium	4	1	1	2
Pneumomediastinum	8	4	5	2**
Pulmonary Interstitial Emphysema	48	25***	24	13***
Death from PAL	7	3	<1	1
Patent Ductus Arteriosus	66	57	54	45*
Necrotizing Enterocolitis	3	3	1	2
Pulmonary Hemorrhage	3	1	<1	1
Congenital Pneumonia	2	3	2	2
Nosocomial Pneumonia	5	7	2	2
Non-Pulmonary Infections	19	22	13	13
Sepsis	15	17	8	8
Death From Sepsis	<1	<1	1	<1
Meningitis	1	<1	1	<1*
Other Infections	5	8	5	6
Major Anomalies	3	3	4	4
Hypotension	62	57	50	39**
Hyperbilirubinemia	17	19	12	10
Exchange Transfusion	3	4	1	2
Thrombocytopenia[b]	10	11	4	<1**
Persistent Fetal Circulation	1	1	6	2**
Seizures	10	10	6	3*
Apnea	48	65**	37	44*
Drug Therapy				
Antibiotics	100	99	98	98
Diuretics	60	65	45	34***
Anticonvulsants	17	17	10	5**
Inotropes	36	31	27	16***
Sedatives	72	68	76	64***
Pancuronium	34	17**	33	15***
Methylxanthines	62	74**	49	53

[a] All parameters were examined with "as-treated" analyses
[b] Thrombocytopenia requiring platelet transfusion
* p<0.05
** p<0.01
*** p<0.001

Pulmonary Hemorrhage. See WARNINGS. **Abnormal Laboratory Values**: Abnormal laboratory values are common in critically ill, mechanically ventilated premature infants. A higher incidence of abnormal laboratory values in the Exosurf Neonatal group was not reported. **Events During Dosing**: Data on events during dosing are available from more than 8800 infants in the open, uncontrolled clinical study (Table 5).

Table 5. Events During Dosing in the Open, Uncontrolled Study[a]

Treatment Type / Number of Infants	Prophylactic Treatment N=1127	Rescue Treatment N=7711
	% of Infants	% of Infants
Reflux of Exosurf	20	31
Drop in O_2 saturation (≥ 20%)	6	22
Rise in O_2 saturation (≥ 10%)	5	6
Drop in transcutaneous pO_2 (≥ 20 mm Hg)	1	8
Rise in transcutaneous pO_2 (≥ 20 mm Hg)	2	5
Drop in transcutaneous pCO_2 (≥ 20 mm Hg)	<1	1
Rise in transcutaneous pCO_2 (≥ 20 mm Hg)	1	3
Bradycardia (<60 beats/min)	1	3
Tachycardia (>200 beats/min)	<1	<1
Gagging	1	5
Mucous Plugs	<1	<1

[a] Infants may have experienced more than one event.
Investigators were prohibited from adjusting FiO_2 and/or ventilator settings during dosing unless significant clinical deterioration occurred.

Reflux: Reflux of Exosurf Neonatal into the endotracheal tube during dosing has been observed and may be associated with rapid drug administration. If reflux occurs, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O until the endotracheal tube clears. ***>20% Drop in Transcutaneous Oxygen Saturation***. If transcutaneous oxygen saturation declines during dosing, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O for 1 to 2 minutes. In addition, increases of FiO_2 may be required for 1 to 2 minutes. ***Mucous Plugs***: See WARNINGS.

DOSAGE AND ADMINISTRATION. See full product information.

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nographic measurements as well as arterial blood gases, pulmonary function, distance walked in 6 minutes, and inspiratory muscle endurance were measured at baseline and after 3 and 14 months of ventilation. Ventilation improved saturation (baseline on O_2; slow-wave sleep (SWS) 87 ± 10, rapid-eye movement sleep (REM) 79 ± 14, ventilator on R/A; SWS 90 ± 6, REM 89 ± 5%) and transcutaneous P_{CO_2} (baseline on O_2; SWS 85 ± 26, REM 94 ± 39, ventilator on R/A; SWS 53 ± 9, REM 58 ± 9 torr). During ventilation, the quantity and distribution of sleep was similar to that observed prior to ventilation. Daytime gas exchange improved as did the 6-min walking test (initial test = 429 ± 120 m, 3 months after ventilation = 567 ± 121 m), both of these improvements being sustained at 14 months. Inspiratory muscle endurance measured using a pressure threshold load (mean mouth pressure = 45% MIP_{RV}) improved from 7.1 ± 3.4 minutes at baseline to 14.8 ± 7.6 minutes at 3 months, an improvement sustained at 14 months. There was no change in measured lung volumes or respiratory muscle strength. We conclude that the improvement in nocturnal gas exchange, daytime functioning, and arterial blood gases resulting from nocturnal positive pressure ventilation is associated with an increase in inspiratory muscle endurance sustained at 14 months.

Hemodynamic Effects of Nasal CPAP Examined by Doppler Echocardiography—JA Leech, KJ Ascah. Chest 1991;99:323.

The effects of incremental application of nasal continuous positive airway pressure (0 to 15 cm H_2O) on heart rate, pulmonary artery pressure, and cardiac index were studied noninvasively by Doppler echocardiography. By two-way analysis of variance within two groups (19 normal volunteers and six sleep apnea patients), no significant effects on heart rate, pulmonary artery pressure, ventricular size, or cardiac index could be found with increasing positive intrathoracic pressures and consequent lung hyperinflation. In subjects with normal cardiac function, nasal CPAP is safe from a hemodynamic viewpoint. This simple, repeatable, and noninvasive technique may be used to assess the clinical safety and efficacy of prescribed nasal CPAP on cardiac hemodynamics in individual patients.

A Disposable End-Tidal CO_2 Detector To Verify Endotracheal Intubation—WR Anton, RW Gordon, TM Jordan, KL Posner, FW Cheney. Ann Emerg Med 1991;20:271.

Study objective: We compared the performance of the Fenem FEF end-tidal CO_2 detector with the TRIMED capnometer to verify endotracheal intubation. *Design:* The FEF indicates the presence of CO_2 by the color change of chemically treated indicator; the TRIMED uses infrared technology. Both devices were used during 60 intubations. *Setting:* Intubations during in-hospital emergency situations outside of the operating room were studied. *Type of participants:* Adult patients undergoing intubation for respiratory failure, CPR, and other airway protection situations were enrolled in the study. *Interventions:* The TRIMED monitor and FEF detector were placed in series between the manual resuscitator and the patient's endotracheal tube adapter after endotracheal tube placement. *Measurements and main results:* We defined the acceptable criterion for detection of CO_2 as production of a positive signal within six manual resuscitator bag breaths. The TRIMED met this criterion in 58 of 60 patients (sensitivity, 0.97) and the FEF met this criterion in 59 of the patients (sensitivity, 0.98). A paired *t* test showed no statistically significant difference in performance between the two devices. In five of nine cases of intubation during CPR, the color change of the FEF was described as "subtle." In one CPR case, a positive signal was not obtained by either device. *Conclusion:* We conclude that the performance of the FEF CO_2 detector is equal to that of the TRIMED monitor for verification of endotracheal intubation in nonCPR situations. Interpretation of FEF color changes during CPR should be approached with caution until further studies using the FEF during CPR are completed.

Ventilation and Gas Exchange during Exercise in Sickle Cell Anemia—P Pianosi, SJA D'Souza, DW Esseltine, TD Charge, AL Coates. Am Rev Respir Dis 1991;143:226.

Adults with sickle cell anemia (SCA) have restrictive lung impairment, increased alveolar dead space, and hypoxemia. These factors, together with increased anaerobic metabolism, are thought to cause exercise hyperventilation. To assess the role of each of these in children, 34 patients with SCA and 16 control subjects performed pulmonary function and exercise tests. Twenty-eight patients with SCA had spirometric values and lung volumes, and all but two patients with SCA had arterial saturation > 91% during exercise. Despite a low $\dot{V}_{O_{2max}}$ (30.07 ± 6.55 mL/min^{-1}/kg^{-1}), the ventilatory anaerobic threshold (VAT) in the patients occurred at a similar $\%\dot{V}_{O_{2max}}$ as in the control subjects (69 ± 9% vs 63 ± 12%). The slope of the $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ relationship for sub-VAT work was steeper in the patients (29.4 ± 6.5 vs 24.7 5.2, p = 0.01), and the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) in steady-state exercise was greater in the patients than in the control subjects (33.2 ± 3.5 vs 30.8 ± 3.5, p = 0.03). End-tidal P_{CO_2} did not differ (38.3 ± 3.0 vs 39.2 ± 3.1), indicating equivalent alveolar ventilation. The patients had a higher dead-space-to-

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tidal-volume ratio (V_D/V_T) than did the control subjects (0.204 ± 0.033 vs 0.173 ± 0.024, $p = 0.0005$). The P_{aCO_2} was significantly lower in those with lower Hb, but there was no difference in pH. In conclusion, children with SCA have an increased exercise ventilatory response caused in part by increased physiologic dead space, and in part by their low Hb. The greater dead space may be the result of sickle cells impairing capillary perfusion to ventilated alveoli.

Airways Inflammation in Nocturnal Asthma—RJ Martin, LC Cicutto, HR Smith, RD Ballard, SJ Szefler. Am Rev Respir Dis 1991;143:351.

Nocturnal asthma is a frequent problem, but the mechanism is unclear. We investigated the possibility that airways inflammation occurred during the night. Bronchoalveolar lavage fluid was analyzed in asthmatic patients with ($n = 7$) and without nocturnal asthma ($n = 7$) at 1600 and 0400 h. The nocturnal asthma group had an increase in the total leukocyte count (24.0 ± 7.0 to $41.1 \pm 9.9 \times 10^4$ cells/mL, $p < 0.05$), neutrophils (1.1 ± 0.6 to $3.7 \pm 1.5 \times 10^4$ cells/mL, $p < 0.05$), and eosinophils (0.5 ± 0.1 to $1.7 \pm 0.7 \times 10^4$ cells/mL, $p < 0.05$) from 1600 to 0400 h. Cellular components for the non-nocturnal asthma group did not change. Between groups, the 1600-h cells were similar. At 0400 h the nocturnal asthma group had significantly higher total leukocyte, neutrophil, eosinophil, lymphocyte, and epithelial cell counts. For all subjects, the overnight fall in peak expiratory flow rates was correlated to the change in neutrophils ($r = 0.54$, $p < 0.05$) and eosinophils ($r = 0.77$, $p < 0.05$). We conclude that the nocturnal worsening of asthma has an associated cellular inflammatory response that is not seen in patients without overnight decrements in lung function. This inflammatory response together with epithelial damage may be important factors in the etiology of nocturnal asthma.

The Effect of Inhaled Corticosteroids on the Maximal Degree of Airway Narrowing to Methacholine in Asthmatic Subjects—EH Bel, MC Timmers, AH Zwinderman, JH Dijkman, PJ Sterk. Am Rev Respir Dis 1991;143:109.

Airway hyperresponsiveness in asthma is characterized by an increase in sensitivity and in maximal response to airway-narrowing stimuli. Long-term therapy with inhaled corticosteroids is known to reduce airway hypersensitivity in asthmatic patients. To investigate whether these drugs also reduce the maximal degree of airway narrowing we studied the effects of inhaled budesonide on the maximal response plateau of the dose-response curve to inhaled methacholine in mildly asthmatic patients in whom a raised plateau could be measured. Sixteen atopic patients with mild asthma were placed randomly into two parallel treatment groups to receive double-blindly either budesonide (400 μg twice daily) or placebo, inhaled via a Turbuhaler, for 4 wk. Before treatment, after 2 and 4 wk of treatment, and after 2 and 4 wk of wash-out, complete dose-response curves to methacholine were obtained using a standardized 2-min tidal breathing method. The response was measured by FEV_1, expressed in % fall from baseline. A plateau on the log dose-response curve was considered if three or more data points fell within a 5% response range. The maximal response was obtained by averaging the values on the plateau ($MFEV_1$), and the sensitivity was calculated from the provocative concentration of methacholine, causing a 20% fall in FEV_1 (PC_{20}). After 4 wk of budesonide treatment, mean $MFEV_1$ decreased from 41.6 to 33.7% fall ($p = 0.0004$). The changes in MFEV were significantly different between placebo and budesonide ($p = 0.0$). The geometric mean PC_{20} increased from 3.4 to 6.3 mg/mL ($p = 0.02$), but the changes in PC_{20} were not different between the two groups ($p = 0.23$). We conclude that budesonide limits the increased maximal airway narrowing in asthmatic patients. The results suggest that asthma therapy should include anti-inflammatory drugs such as inhaled corticosteroids in order limit potentially dangerous degrees of airway narrowing.

Accuracy of Flexible Fiberoptic Endoscopy in Identifying Abnormal Endotracheal Tube Positions—KA Dietrich, SA Conrad, MD Romero, JL Lloyd, EE Fontenot. Pediatr Emerg Care 1990;6:257.

This study was carried out to investigate the accuracy of a simple, nonmaneuverble, flexible fiberoptic catheter in identifying both normal and abnormal endotracheal tube (ETT) positions. In addition, the utility of flexible fiberoptic endoscopy (FFE) for ETT position determination in inexperienced hands was examined. One adult dog was sedated and instrumented in the esophagus and trachea with identical ETTs. Four possible ETT positions (trachea, carina, bronchus, esophagus) were randomly assigned. One investigator positioned the ETT into the assigned position by fluoroscopy. Four other blinded investigators were asked to determine the ETT position using the fiberoptic catheter. Each blinded investigator was given 15 seconds to complete the examination and record the ETT 'position. Randomization resulted in 25 ETT positions examined by each of the four blinded investigators for a total of 100 FFE determinations. FFE ETT determination was correct in 97% of the examinations. All esophageal intubations were correctly identified. Two tracheal locations were misdiagnosed as carina and bronchial, while one carinal location was 91.7%, and the specificity was 98.6%. There was no difference in performance by inves-

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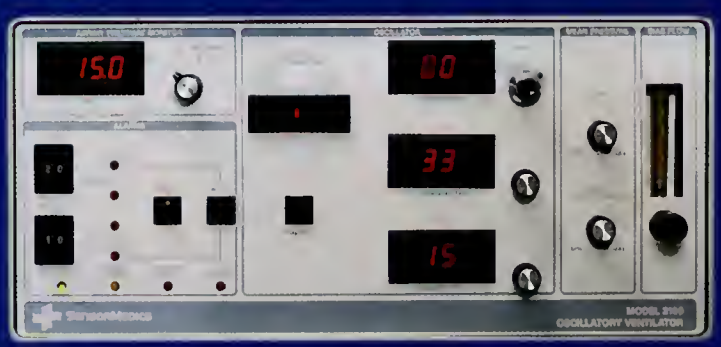

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1 High-Frequency Oscillatory Ventilation Reduces the Incidence of severe Chronic Lung Disease in Respiratory Distress Syndrome. Reese Clark, MD, D. Gerstman, D. Null, R.A. Jeheimes. American Review of Respiratory Disease, April 1990.

2 High Frequency Oscillation Decreases the Incidence of Air Leak Syndrome in Infants with Severe Respiratory Distress Syndrome. HIFO Study Group, Snowbird High Frequency Conference, 1991.

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tigator training level or endoscopy experience. We conclude that FFE is a rapid and accurate method for determining both normal and abnormal ETT locations. ETT position determination can be confidently performed by health professionals with minimal training.

Metered Dose Inhalers for Bronchodilator Delivery in Intubated, Mechanically Ventilated Patients—PC Gay, HG Patel, SB Nelson, B Gilles, RD Hubmayr. Chest 1991; 99:66.

We determined the relative efficacy of two bronchodilator aerosol delivery methods in 18 intubated mechanically ventilated patients with airways obstruction. Two treatment arms, consisting of albuterol 270 μg (three puffs) from a metered dose inhaler and albuterol 2.5 mg from a saline solution nebulized with an updraft inhaler, were compared in a single blind, randomized crossover design. Pulmonary function was evaluated using an interrupter technique. Changes in passive expiratory flow at respiratory system recoil pressures between 6 and 10 cm H_2O provided the therapeutic endpoints. Paired measurements were made before and 30 minutes after drug delivery. The MDI and NEB resulted in similar improvements in iso-recoil flow (mean increase for both groups = 0.1 L/s). Treatment sequence, severity of obstruction, and brochodilator responsiveness had no effect on relative efficacy. Albuterol caused a small but significant increase in heart rate that was similar following both delivery methods. We conclude that bronchodilator aerosol delivery with metered dose inhalers provides a viable alternative to nebulizer therapy in intubated mechanically ventilated patients and may result in a cost savings to hospitals and patients.

Measurement of Minute Ventilation in Ventilator-Dependent Patients: Need for Standardization—KL Yang, MJ Tobin. Crit Care Med 1991;19:49.

Objectives: (a) To determine the variation in methods used to measure minute ventilation ($\dot{V}_E$) in patients who receive mechanical ventilation; (b) to determine the effect of supplemental oxygen on $\dot{V}_E$, respiratory rate (RR), and tidal volume (V_T) measurements. *Design:* Telephone survey of hospitals, and a randomized control trial. *Setting:* Medical and surgical ICUs in a university hospital. *Patients:* Thirty-three patients who had required mechanical ventilation because of the inability to sustain adequate spontaneous ventilation. All patients were considered ready to undergo a weaning trial by their physicans. *Interventions:* Spontaneous $\dot{V}_E$, RR, V_E and S_{aO_2} were measured both in the presence and absence of supplemental oxygen; measurements were obtained in a randomized manner. *Measurements and Main Results:* (a) In a telephone survey of hospitals throughout the country, we found that the measurement of $\dot{V}_E$ is variably obtained during room air breathing or in the presence of supplemental oxygen. (b) Measurements of $\dot{V}_E$ increased from 11.0 ± 0.8 L/min while patients received supplemental oxygen to 13.5 ± 1.1 L/min while patients breathed room air ($p < 0.001$). Of 15 patients who had a $\dot{V}_E < 10$ L/min while receiving supplemental oxygen, seven developed a value > 10 L/min while breathing room air; thus, a weaning trial might have been inappropriately deferred in these patients. (c) Mean S_{aO_2} decreased from $95.0 \pm 0.6\%$ while breathing supplemental oxygen to $90.2 \pm 1.1\%$ while breathing room air ($p < 0.001$). *Conclusions:* Measurements of $\dot{V}_E$ in patients being considered for a weaning trial can result in significant oxygen desaturation if obtained during room air breathing, and the values obtained can significantly overestimate the patient's true ventilatory requirements, since most patients receive supplemental oxygen during a weaning trial. Standardized methods of measuring $\dot{V}_E$ in critically ill patients need to be developed.

Interpretation of the Alveolar-Arterial Oxygen Difference in Patients with Hypercapnia—BA Gray, JM Blalock. Am Rev Respir Dis 1991;143:4.

According to conventional wisdom, the difference between alveolar and arterial O_2 tensions, the $P_{(A-a)O_2}$, should distinguish between hypoxemia caused by alveolar hypoventilation and hypoxemia caused by alveolar hypoventilation complicated by other abnormalities of gas exchange. To test this concept we have calculated the $P_{(A-a)O_2}$ from arterial blood gas measurements, breathing air, in 23 patients with hypercapnia, hypoxemia, and advance obstructive lung disease (mean $FEV_1 = 0.88$ L). We found that $P_{(A-a)O_2}$ varied inversely with P_{aCO_2} ($r = -0.83$, $p < 0.001$). In five of these patients with the most severely elevated P_{aCO_2} (range, 59 to 81 torr) the $P_{(A-a)O_2}$ was within normal limits. We also calculated the difference between the O_2 contents of 'ideal' pulmonary capillary blood and arterial blood and expressed this as the venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) based on an assumed arteriovenous content difference of 4.5 mL/dL. In contrast to the $P_{(A-a)O_2}$, the $\dot{Q}_{VA}/\dot{Q}_T$ was abnormal in all patients (mean = 41 ± 8%). We conclude that the $P_{(A-a)O_2}$ may be an unreliable indicator of abnormal gas exchange in the presence of alveolar hypoventilation. This finding can be explained by substantial changes in the position of the alveolor and arterial points on the oxygen dissociation curve for hemoglobin in the presence of alveolar hypoxia secondary to hypoventilation.

Asthma in the Elderly: A Comparison Between Patients with Recently Acquired and Long-standing Disease—SS Braman, JT Kaemmerlen, SM Davis. Am Rev Respir Dis 1991;143:336.

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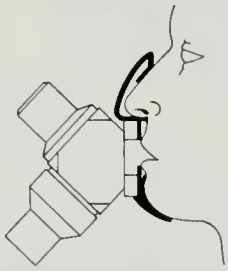

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1. Bronchodilators Effect of Fenoterol and Ipratropium Bromide in Infants With Acute Wheezing: Use Of MDI With A Spacer Device. Mallol, J., Barrueto, L. Girardi, G. and Toro, O. Pediatric Pulmonology 5:352-356 (1987)

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To characterize asthma in the elderly, 25 consecutive nonsmoking pulmonary clinic patients over the age of 70 who met the American Thoracic Society criteria for asthma were identified. Of these, 12 patients (48%) had developed asthma at an advanced age (> 65 yr). This group with late-onset asthma had a mean duration of disease of 5.1 ± 2.5 y. The remaining group with early-onset asthma had a mean duration of illness of 31.4 ± 14.6 y. On the day of evaluation each patient underwent pulmonary function testing off all medication for at least 12 h. These two groups were indistinguishable by symptoms and medication requirements. Immediate hypersensitivity skin testing to 43 aeroallergens was uniformly negative in all 25 patients but the histamine control was always positive. IgE levels in both groups were not different from those in elderly control subjects. Those with early-onset asthma had a greater likelihood of previous allergic disease ($p < 0.001$) and a significantly greater degree of airflow obstruction in pre- and postbronchodilator pulmonary function testing ($p < 0.05$). This study suggests that long-standing asthma may lead to chronic persistent airflow obstruction and thereby mimic chronic bronchitis and emphysema (COPD).

Exercise Performance and Breathing Patterns in Cystic Fibrosis: Male-Female Differences and Influence of Resting Pulmonary Function—DM Orenstein, PA Nixon. Pediatr Pulmonol 1991;10:101.

Despite improved prognosis for patients with cystic fibrosis (CF), they continue to suffer from progressive decline in pulmonary function and exercise tolerance. Beyond puberty, female patients have greater loss of pulmonary function and higher mortality than males, yet no one has studied male-female differences in exercise tolerance among patients. We therefore compared the responses to progressive exercise in 58 male and 52 female patients with CF and analyzed the influence of resting pulmonary function and gender on these responses and on breathing patterns during exercise. Within each of three pulmonary function groups (group 1: $FEV_1 \geq 65\%$ predicted; group 2: $FEV_1 = 50\text{-}64\%$ predicted; and group 3: $FEV_1 < 50\%$ predicted), female patients had lower exercise tolerance than males. This was reflected in the overall group for each gender: males' peak work load was 130 ± 64 W, females' 111 ± 32 W ($p = 0.04$); males' peak oxygen consumption, 36.9 ± 11.4 $mL \cdot kg^{-1} \cdot min^{-1}$ and females', 31.0 ± 7.4 $mL \cdot kg^{-1} \cdot min^{-1}$ ($p = 0.0006$). There was no interactive effect between gender and pulmonary function. Neither respiratory rate nor tidal volume differed between sexes. Male and female patients, irrespective of disease severity, employed similar proportions of their ventilatory capacity at exhaustion; group mean minute ventilation to maximum voluntary ventilation ratio ranged from 62.9 to 78.3%, with no apparent relationship to disease severity.

Effect of Ethanol on the Efficacy of Nasal Continuous Positive Airway Pressure as a Treatment for Obstructive Sleep Apnea—RB Berry, MM Desa, RW Light. Chest 1991;99:339.

The effect of ethanol ingestion on the efficacy of nasal continuous positive airway pressure (nasal CPAP) as a treatment for the obstructive sleep apnea (OSA) syndrome was studied in ten obese male subjects undergoing this therapy. On the first night of polysomnography, the lowest level of CPAP that maintained airway patency was determined (critical level). On the second (control) night (C), subjects slept the entire night on this level of CPAP. On the third night (E), subjects ingested either 1.5 mL/kg (part A, N = 6) or 2.0 mL/kg (part B, N = 4) of 50 percent ethanol (100 proof vodka) over one half-hour starting 1 h before bedtime. A serum ethanol level was obtained at bedtime (part A: 63.7 ± 17.3 mg/dL; part B: 108.6 ± 20.6 mg/dL), and subjects were monitored on the critical level of CPAP. Comparison of nights C and E for parts A + B showed no difference in total sleep time (TST) or the amount of different sleep stages as an absolute time or a percentage of TST except that there was more stage 2 (as a percent of TST) on E nights. The apnea + hypopnea index and C and E nights did not differ and was quite low (3.6 ± 3.7/h vs 1.9 ± 2.7/h). Similarly, ethanol ingestion did not increase the number of desaturations to at or below 90 and 85 percent, or lower the mean arterial oxygen saturation in NREM or REM sleep. Analysis of parts A and B separately also showed no differences with respect to the apnea + hypopnea index or the number of desaturations on control and ethanol nights. We conclude that acute moderate ethanol ingestion does not decrease the efficacy of an optimum level of nasal CPAP.

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Accolades for Publication: The ARCF Awards Program

The American Respiratory Care Foundation (ARCF), affirming the validity of the notion that one of the marks of a profession is the literature unique to it, is establishing an ongoing awards program to foster and reward practitioner publication in RESPIRATORY CARE. The awards for 1991 are made possible through the generosity of Allen & Hanburys, Division of Glaxo Inc.

Specifically, for 1991 the Allen & Hanburys Awards are:

(1) $2,000 for the best original paper (study, evaluation, or case report) accepted for publication from November 1990 through October 1991. This award is not confined to papers based on Open Forum presentations.

(2) Four awards of $1,000 each for papers accepted for publication from November 1990 through October 1991 based on 1990 Open Forum presentations.

(3) Five awards of $500 each for the best papers submitted (not published) from 'never published' in RESPIRATORY CARE 1991 Open Forum participants. The author must present the abstract at the Annual Meeting and must submit a paper based on the abstract *before* the Annual Meeting (received in the Editorial Office by December 1).

As was the case in 1990, any 1991 Open Forum presenter (or co-author designee) will receive complimentary registration for a paper based on his 1991 Open Forum abstract, submitted prior to or at the 1991 Annual Meeting.

A given paper (and author) is not eligible for both (1) and (2). The third category is clearly confined to submissions from Open Forum participants who have never published in RESPIRATORY CARE. They may contend for (1) and (2) in subsequent years.

Critics may ask, Why dangle the carrot of a $500, $1000, or $2000 award in front of an investigator's nose? Like art, isn't research for research's sake enough? Isn't publication itself enough? Perhaps—but respiratory care research is rarely funded by grants, and many researchers gather data and write papers not 'on the clock' of a funded research position but on their own time sandwiched into an already demanding schedule. For many, clerical support is nonexistent.

The body of knowledge built bit by bit from the observations of its practitioners is important to the respiratory care profession. Implementing a sound study design and gathering data can be difficult, but writing and revising the related paper is plain hard work. Data never legitimized by peer review and publication is 'wasted.' With the Allen & Hanburys Awards, the ARCF seeks to encourage researchers to convert 'the abstract to the concrete.' One need only glance through the pages of Annual Meeting Programs or Convention issues of the Journal to see the evidence of wasted data, of good work begun yet never completed. Although some studies reported in abstracts turn out to be too weak to ever be published as full papers (ie, they will fail to pass the scrutiny of reviewers), many sets of adequate and potentially valuable data die aborning simply because the studies and data have never been fully reported and submitted for publication.

Allen & Hanburys, the ARCF, the Association, and the Journal's Editorial Board and Staff seek to encourage that 'final mile' of paper preparation and submission. Evidence of the vision of the profession and the Association's early leaders is the continued presence of RESPIRATORY CARE, which has recognized, refereed, and recorded such observations for almost as long as the profession has existed. So, it is appropriate that the ARCF use the vehicle of the Journal to further the development of that body of knowledge and unique literature. The

Journal's Editorial Board and Staff have over the years demonstrated their willingness to help authors with manuscript preparation and revision, and they are committed to continuing to do so.

How will choices be made? By the consensus of the same ARCF contingent that reviews grant and scholarship requests.

When will awardees be notified? Prior to the Annual Meeting, to allow honorees to be present at the Awards Ceremony.

Do candidates need to make formal application? No, all published papers in each category will be judged automatically. However, authors should note their eligibility for specific categories in their cover letter to avoid any possibility of being overlooked.

What is the source of the funding for the awards? Generous 'no-strings' educational grants from Allen and Hanburys. However, the grants are just that—no strings—and the donors will not dictate content, review papers, or participate in the selection process in any way.

Carrots? Perhaps. Awards for merit? Absolutely!

Pat Brougher
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Part I

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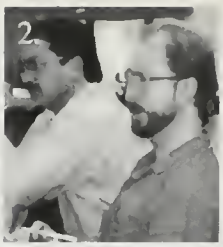

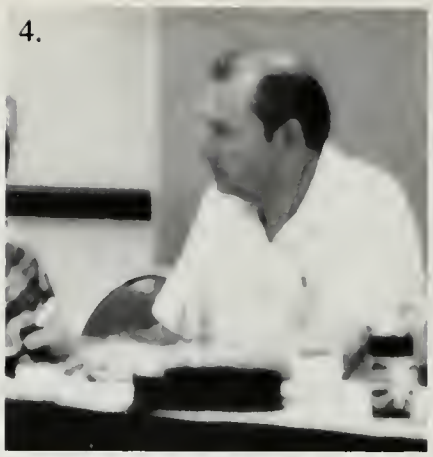

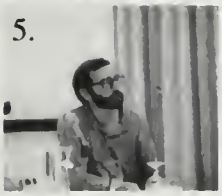

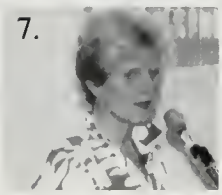

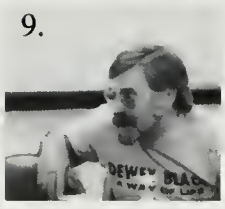

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Neonatal and Pediatric Respiratory Care: Some Implications for Adult Respiratory Care Practitioners

Dean Hess MEd RRT

It is axiomatic that there are important differences in the respiratory care of adults, children, and neonates. Differences exist in anatomy, pathophysiology, and treatment, and these differences make it increasingly difficult for the respiratory care generalist to remain expert in all aspects of respiratory care from neonatology to geriatrics. However, there is also overlap between the care of neonates, children, and adults (Fig. 1). Within the past 5-10 years there has been an increasing tendency for respiratory care practitioners to specialize in neonatal and pediatric respiratory care; as a result, in 1991, the National Board for Respiratory Care (NBRC) began administering a perinatal-pediatric specialty examination.

I am primarily an adult-care practitioner and clinical researcher. As such, it may at first seem inappropriate that I write a paper such as this. However, I believe that practitioners of adult respiratory care can learn much from neonatal and pediatric respiratory care. Many of the patients seen by practitioners of neonatal and pediatric respiratory care will be seen later in life by adult-care practitioners. Some diseases that begin in childhood, such as asthma and cystic fibrosis, may continue into adulthood. Also a number of technologic advances in neonatal and pediatric respiratory care have later affected adult respiratory care.

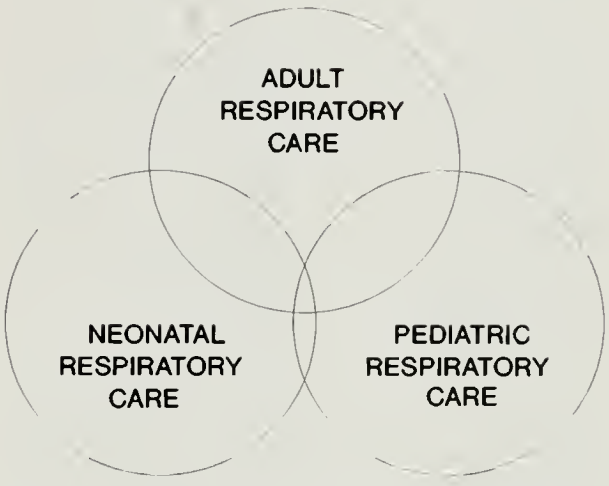

Fig. 1. Overlap among neonatal respiratory care, pediatric respiratory care, and adult respiratory care.

Postnatal Pulmonary Growth and Development

Considerable cell multiplication and development in the lung occurs following birth.[1-5] At birth, the mass of the human lung is about one tenth of the mass of the adult lung. Interestingly, the volume of the lung increases more than its mass so that it progressively contains more air per gram of tissue. The lungs increase in mass from 60 g at birth to 750 g in the adult, and in volume from 250 mL at birth to 6000 mL in the adult.

A considerable increase in the number of alveoli occurs from birth to adulthood (Fig. 2). In the early

Mr Hess is Assistant Director of Research, York Hospital, and Instructor, School of Respiratory Therapy, York Hospital and York College of Pennsylvania, York, Pennsylvania.

A version of this paper was presented by Mr Hess on December 13, 1990, at the RESPIRATORY CARE Journal Conference on Respiratory Care of Infants and Children held in Cancun, Mexico.

Reprints: Dean Hess MEd RRT, Assistant Director of Research, York Hospital, 1001 S George St, York PA 17405.

Abbreviations Used in This Paper

ARDS	—	Adult respiratory distress syndrome
BPD	—	Bronchopulmonary dysplasia
CF	—	Cystic fibrosis
COPD	—	Chronic obstructive pulmonary disease
CPAP	—	Continuous positive airway pressure
CPT	—	Chest physiotherapy
CRT	—	Childhood respiratory trouble
ECMO	—	Extracorporeal membrane oxygenation
FET	—	Forced expiration technique
HFV	—	High-frequency ventilation
HFOV	—	High-frequency oscillatory ventilation
ICU	—	Intensive care unit
LFPPV-ECCO$_2$R	—	Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal
MDI	—	Metered-dose inhaler
NBRC	—	National Board for Respiratory Care
PCIRV	—	Pressure-controlled inverse-ratio ventilation
PEP	—	Positive expiratory pressure
RDS	—	Respiratory distress syndrome
RSV	—	Respiratory syncytial virus

1960s, Dunnil[15] estimated on the basis of data from a single newborn lung that about 24 million alveoli are present at birth, compared to about 300 million alveoli in the adult lung. More recently (1984), Langston et al[6] studied 42 infants and found the mean number of alveoli at birth to be 50 million (with SD of 7.76 million and range 9.60-148.84 million). Although some disagreement among investigators exists over the number of alveoli present at birth,[3] all agree that the greatest increase in alveolar numbers occurs during the first 2 years of life. Alveolar multiplication slows considerably

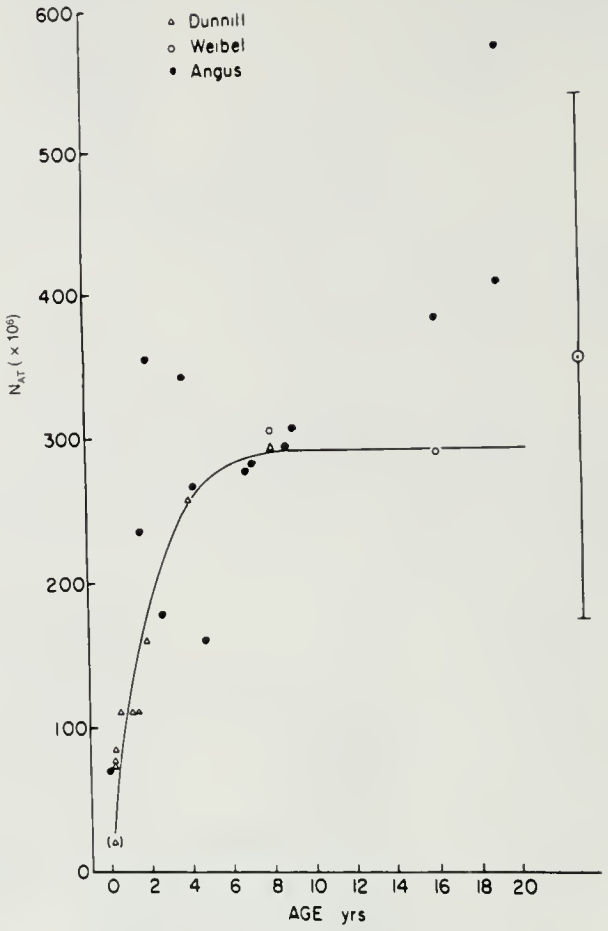

Fig. 2. The total number of alveoli (N_{AT}) plotted against age, as found by different investigators. The range in normal adults is shown at the right (from Reference 4).

by about 8 years of age, but may not cease until somatic growth stops. Alveolar multiplication, more than alveolar enlargement, contributes to the increase in lung volume that occurs during childhood. Lung volume increases about 25 times, the number of alveoli increases by about 10 times, and the intra-alveolar distance increases by about one third. Although it is well known that alveoli multiply for some years following birth, very little is known about how this relates to early childhood disease.

It is also of interest to compare the resistance to gas flow through central and peripheral airways in children and adults. Using a retrograde-catheter technique, Hogg et al[7] have reported that the resistance to gas flow through central airways changes very little with age. Resistance through peripheral airways, however, decreases considerably

(ie, conductance increases) at about 5 years of age (Fig. 3). In other words, the bronchioles of small children are responsible for a greater proportion of total resistance than are the bronchioles of adults. This has been used to explain the greater prevalence of diseases such as bronchiolitis in children < 5 years of age.

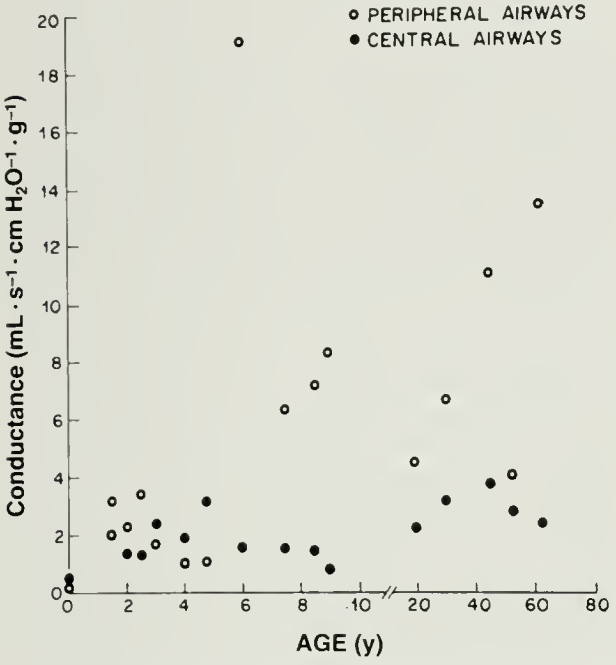

Fig. 3. Change in conductance of central and peripheral airways per gram of lung tissue with age. (Adapted, with permission, from data in Reference 7.)

Pores of Kohn and Canals of Lambert are deficient both in size and number in the infant lung.[8] For this reason, obstructive lung disease may be more likely to lead to patchy atelectasis in infants.

From a respiratory care standpoint, it is of value to know at what age bronchospasm first occurs. In a morphometric study, Matsuba and Thurlbeck[9] found that the proportion of muscle in the major bronchi was the same in children and in adults, but the proportion of muscle in the small airways was smaller in children than in adults. Lenney and Milner[10] evaluated the response to nebulized salbutamol in 32 wheezing children aged 7 months to 43 months. They found that no child under 18 months showed a drop in airways resistance > 5 %, suggesting that these children did not respond to salbutamol with bronchodilation. Studies such as this lead some to believe that bronchial smooth muscle is not present in children under 18 months of age; however, others have found results contradictory to this. Tepper[11] studied 10 healthy male infants with a mean age of 8.1 months (range 3.5-14.5 months) by measuring the response to methacholine and metaproterenol. He found that use of methacholine resulted in decreased expiratory flow in the infants, and that the flows returned to baseline following administration of metaproterenol (Fig. 4). Motoyama et al[12] found a severe degree of lower airway obstruction in premature infants who had developed bronchopulmonary dysplasia by 3-4 weeks of postnatal age. Inhalation of nebulized isoetharine was associated with a dramatic increase in expiratory flow. The most premature infant with demonstrated airway reactivity in that study was 26 weeks postconception, and the youngest was 12 days old. These results suggest that infants do develop bronchospasm and that this bronchospasm is responsive to aerosolized bronchodilators. Others have reported airway responsiveness in infants to challenges with histamine[13,14] and cold, dry air.[15]

Neonatal and Pediatric Respiratory Disease

Respiratory Distress Syndrome

The respiratory distress syndrome (RDS) in infants, which has also been called hyaline membrane disease (HMD) and idiopathic respiratory distress syndrome (IRDS), is a common cause of morbidity and mortality in premature infants.[16-19] In the United States, nearly 5,000 infants die each year due to RDS. As an adult-

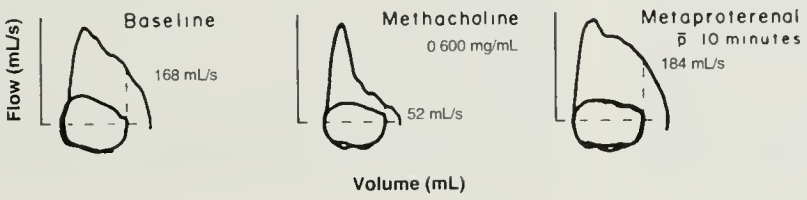

Fig. 4. An illustration of the change in the expiratory flow curve of an infant at baseline, after administration of methacholine, and after administration of metaproterenol. (Reprinted, with permission, from Reference 11.)

care practitioner, it is of interest to me to contrast infant RDS with the adult respiratory distress syndrome (ARDS) (Table 1).[20-28] Both infant RDS and ARDS result in shunting, hypoxemia, and decreased lung compliance. Both are treated with positive-pressure ventilation, and both are associated with a relatively high mortality rate. However, the pathophysiology of infant RDS is associated with a deficiency of surfactant in the immature lung, whereas ARDS is usually associated with an insult to the lung such as occurs with sepsis, aspiration, or trauma. A significant number of infants with RDS who survive develop the chronic disease bronchopulmonary dysplasia (BPD). On the other hand, patients with ARDS who survive usually do not develop chronic pulmonary disease. In spite of the similarities between infant RDS and ARDS, they are quite different disease processes.

Table 1. Comparison of RDS and ARDS

RDS	ARDS
Surfactant deficiency	Insult to lung parenchyma
Decreased lung compliance	Decreased lung compliance
Intra-/extrapulmonary shunting	Intrapulmonary shunting
Hypoxia	Hypoxia
Responds to positive pressure	Responds to positive pressure
High mortality	High mortality
Chronic pulmonary disease (BPD) common following resolution	Chronic pulmonary disease rare following resolution

It is of interest to note that ARDS can occur in pediatric patients.[29-33] ARDS in pediatric patients occurs in the same form as it does in adults. ARDS has been noted in pediatric patients as young as 2 weeks of age. Pediatric ARDS may occur at a rate of 8.5-10.4 cases per 1,000 pediatric intensive-care-unit admissions, and may have a mortality rate as high as 60%. Treatment for ARDS in children, as in adults, is supportive and includes supplemental oxygen administration, positive-pressure ventilation, and PEEP. In ARDS, structural and functional derangements are partially reversible, and residual abnormalities are minimal.[33-37] However the long-term sequelae of surviving ARDS may be more common and more serious in children than in adults.[38]

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia was first described by Northway et al[39] in 1967 and since then has become recognized as an important neonatal and pediatric respiratory disorder.[40-48] Although strict definitions of BPD differ, a liberal definition includes all patients who remain oxygen dependent for more than 28 days following mechanical ventilation during the first weeks of life, and who have persistent increased densities on chest radiograph. Although the exact incidence is unknown, it is probably about 10-20% of all infants with RDS who require mechanical ventilation.[49,50] It has been suggested that as many as 35,000 infants may develop BPD each year in the United States.[43] BPD typically develops in premature infants who require oxygen therapy and positive-pressure ventilation. Once it has developed, infants require mechanical ventilation and oxygen therapy for prolonged periods of time.

Patients with BPD have chronic pulmonary disease. Clinically they are chronically hypoxemic, oxygen-dependent, and hypercapnic; have cor pulmonale, frequent respiratory tract infections, hyperinflation, atelectasis, and wheezing; require frequent rehospitalizations; and are at risk for sudden infant death syndrome (SIDS). Many of these patients are discharged from the hospital on long-term home oxygen. In some ways, BPD clinically resembles chronic obstructive pulmonary disease (COPD).

The long-term outcome of infants with BPD is unknown. Several studies[51-55] conducted on children who had BPD in infancy suggest that long-term respiratory dysfunction may be a consequence of BPD. Bronchial hyperreactivity may be a problem in these children.[55] Because the oldest survivors of BPD are not yet 20 years of age, the adult sequelae of the disease are not known; however, it is reasonable to expect that some survivors of BPD may carry long-term sequelae into adulthood.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common genetic disease of Caucasian populations.[56-68] The incidence of CF is about one in 2,000 live births, and the frequency of carriers of the gene is about 1 in 20.[69] The recent discovery of the CF gene opens the possibilities of gene therapy and the development of an animal model to study the disease.[68] CF is a multisystem disease, affecting exocrine glands throughout the body. CF is responsible for most cases of progressive chronic respiratory disease in the first 3 decades of life, most cases of severe intestinal malabsorption in children, and most of the pancreatic insufficiency and intestinal obstruction due to meconium ileus in newborns. CF is also associated with many cases of cirrhosis of the liver, rectal prolapse, and nasal polyps.

Although CF was once regarded exclusively as a disease of newborns and small children, it must now also be considered a disease of young adults.[70-76] In 1968 the median survival of CF patients was about 7 years, but it is now approaching 30 years. The reasons for this may be multifactorial but are probably related to earlier diagnosis and improved treatment. Because of this increased survival, clinicians who care for adult patients need to be familiar with the care of CF patients. Although most CF cases are diagnosed in infancy and early childhood, an increasing number of cases are not recognized until adulthood. Huang et al[76] found that 5% of 142 CF patients in their series were diagnosed between the ages of 16 and 30 years.

A number of complications may exist in the adult CF patient that don't exist in the pediatric CF patient (Table 2).[71] Digital clubbing is present in almost all adults with CF, and a number of these patients develop pulmonary hypertrophic osteoarthropathy. Nasal polyps are present in 48% of adults with CF, and may be a presenting manifestation of the disease before apparent pulmonary disease. Sinusitis is present in 90% of adults with CF and hemoptysis in 5-10%.[77] Although spontaneous pneumothorax rarely occurs in children less than 10 years of age who have CF, it may occur in as many as 20% of CF patients over the age of 14 years. Intestinal obstruction, cirrhosis, and glucose intolerance are also associated with CF in adults. About 95% of men and boys with CF are sterile. Women and girls with CF can become pregnant, and over 150 pregnancies of CF patients have been reported. The mortality of pregnant women with CF is no higher than the mortality of nonpregnant women with CF; however, there is a higher than expected rate of preterm births, perinatal deaths, and maternal complications among CF women.[78]

Table 2. Complications of Cystic Fibrosis in Adult Patients*

Complication (% of Patients)	Treatment
Pulmonary hypertrophic osteoarthropathy (5%)	Analgesics, anti-inflammatories
Nasal polyps (48%)	Topical nasal steroids, surgery
Sinusitis (90%)	Antibiotics, surgery
Hemoptysis (5-10%)	Antibiotics, transfusion, bronchoscopy, embolization, lobectomy
Pneumothorax (19%)	Chest tube, obliteration of pleural space
Intestinal obstruction (17%)	GoLytely or Colyte solution; Hypaque or Gastrographin enema
Cirrhosis (2-5%)	Shunt if portal hypertension
Glucose intolerance (9%)	Diet, insulin
Infertility in males (95%)	Counseling

*Adapted, with permission, from Reference 71.

Pediatric Asthma

Using the definition recommended by the American Thoracic Society,[79] asthma is a disease characterized by increased responsiveness of the airways to various stimuli that is manifested by widespread narrowing of the airways, which changes in severity either spontaneously or in response to therapy. Asthma is a disease that occurs in infancy, childhood, and adulthood (Fig. 5).[80-82] In 1988, 4,580 persons died of asthma in the United States.[83] Asthma mortality has increased slightly over the past decade (Fig. 6). The asthma death rate in blacks is almost three times greater than that in whites.

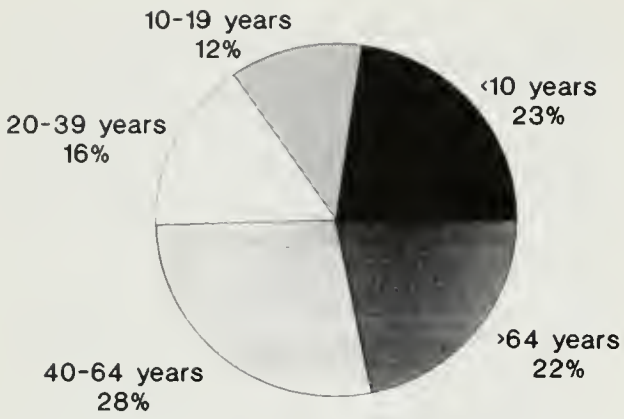

Fig. 5. Distribution of physician visits for asthma by patient age from July 1988 to June 1989. (Adapted, with permission, from data in Reference 82.)

The onset of childhood asthma usually occurs in the first few years of life. One third of these children will have their first symptoms before the age of 2 years, and 80% will develop symptoms before the age of 5 years.[83-88] An estimated 5-10% of children experience asthma. The mortality of pediatric asthma is relatively low; about 400 young persons between the ages of 5 and 34 years died of asthma in 1985 in the United States.[89] Asthma is the leading cause of childhood disability, and its prevalence, morbidity, and mortality have been increasing. Asthma is a major cause of school absenteeism. In Baltimore, Mak et al[90] found that nearly 50% of children with active disease missed 6 days or more of the school year due to their asthma. Prior to puberty, asthma is more prevalent in boys than in girls, but this sex ratio may reverse in older children. The tendency or predisposition for childhood asthma is often inherited, but the inheritance is complex and is probably multifactorial and polygenic.

Asthma has been classically categorized as either extrinsic asthma or intrinsic asthma.[91] In extrinsic asthma, patients tend to be younger, and to have a personal and family history of allergy, increased sputum and blood eosinophils, increased serum IgE, and positive skin tests for a variety of allergens. In intrinsic asthma, the patients are older, with no history of allergy. Sputum eosinophils, but not serum eosinophilia, may be present, and skin tests for allergens are nonspecific. Extrinsic asthma tends to be stimulated by allergens, whereas intrinsic asthma tends to be stimulated by viral infection. Intrinsic asthma tends to be more difficult to treat than extrinsic asthma. Although many pediatric asthmatics tend to have an extrinsic asthma, intrinsic factors are often important as well.

Asthma is probably a disease of infants as well as children and adults. However, many clinicians do not consider infants who wheeze in response to respiratory tract infection to be asthmatic.[80,81] These infants are often referred to as having "wheezy bronchitis," "asthmatic bronchitis," "pseudoasthma," or "spastic bronchitis." It has recently been suggested[83] that infants with recurrent wheezing have a common underlying basic disorder, regardless of the precipitating cause and should be called asthmatic. In infants, the most common precipitant of wheezing is viral infection, and the most common virus is the respiratory syncytial virus (RSV). RSV is also a common cause of bronchiolitis infants 2-6 months of age. It has been suggested[83] that infants with repeated attacks of bronchiolitis should be considered asthmatic. In children, as well as adults, it is important to appreciate that all that wheezes is not asthma. In infants with first-time wheezing, it is important to consider other causes of wheezing such as bronchiectasis and congenital vascular anomalies.

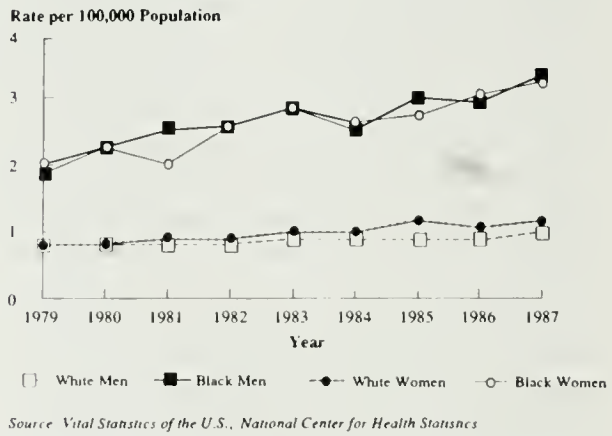

Fig. 6. Trends in asthma mortality, U.S. age-adjusted death rates, 1979-1987. (Reprinted, with permission, from data in Reference 82.)

The lay public and, perhaps, many health-care practitioners believe that most children with asthma

will outgrow their disease during adolescence. However, many persons with childhood asthma will carry the disease with them into adulthood.[84,85,92] It may be that children outgrow their pediatricians rather than their asthma. Many asthmatics seen by pediatric-care practitioners will be seen by adult-care practitioners later in life. Long-term remission may occur in many pediatric asthmatics, with the likelihood of long-term remission being greatest in children with mild disease.

Pediatric asthma is a psychosocial as well as respiratory disease, affecting the family as well as the asthmatic.[93,94] A number of successful programs have been developed to address the psychosocial aspects of this disease, including the "Superstuff" education program available through the American Lung Association, community family asthma education and support programs, and summer asthma camps.[95]

Croup and Epiglottitis

Croup is the most common cause of airway obstruction in children,[96-100] and occurs primarily in children 3 months to 5 years of age (mean 18 months) because of the very small size of the cricoid ring and other subglottic structures in these children. Croup is most commonly caused by a viral infection (eg, parainfluenza virus Type I) in the subglottic region of the larynx. The occurrence of croup is seasonal, with an increase in cases beginning in autumn and continuing into the winter months. Croup often follows an upper-respiratory tract infection. Signs of croup include a 'croupy' barking cough, stridor, dyspnea, nasal flaring, varying amounts of fever, and minimal-to-severe labored breathing. Although many children with croup do not require hospitalization, it does account for about 20,000 hospital admissions per year in the United States.[99] The treatment of croup often involves the use of humidified air or oxygen and aerosolized racemic epinephrine. Of those children hospitalized with croup, 1-5% require intubation.[99]

Epiglottitis is much less common than croup.[100,101] In contrast to croup, epiglottitis is an acute, rapidly progressing, fulminant bacterial inflammation of the supraglottic structures. Epiglottitis quickly produces inspiratory airway obstruction, requiring intubation or tracheostomy. It is usually caused by *Hemophilus influenza* and occurs in children 2 to 7 years of age. Children with epiglottitis have dysphagia, drooling, dysphonia, and inspiratory respiratory distress (sometimes called the four Ds). Laryngoscopy is often not recommended because it can worsen the airway obstruction, and lateral neck radiographs are often not recommended because they can delay the securing of a patent airway. As soon as the diagnosis of pediatric epiglottitis is made, the patient should be transferred to the operating room where intubation or, if necessary, tracheotomy can be performed. Appropriate antibiotics are also used in the treatment of epiglottitis.

It is not often appreciated that epiglottitis can affect adults as well as children. Over 500 cases of adult epiglottitis have been reported in the literature.[102] A number of recent reviews have drawn additional attention to the occurrence of adult epiglottitis,[102-112] and it has been speculated that George Washington may have died from epiglottitis.[102,103] Adult epiglottitis may be commonly misdiagnosed in the emergency department. Signs and symptoms of adult epiglottitis include sore throat, dysphagia, respiratory distress, muffled voice or hoarse speech, drooling, and stridor. In contrast to pediatric epiglottitis, adult epiglottitis often takes a much more benign course. Although those caring for adult patients with epiglottitis should be prepared to secure an airway by intubation or tracheostomy, airway management is often not required. Indirect laryngoscopy and lateral neck radiographs can be used to make the diagnosis. Although *Hemophilus influenza* is often associated with adult epiglottitis, the organism is not isolated from blood or pharyngeal secretions in many of these patients. Many adults with epiglottitis can be treated medically with intravenous antibiotics, steroids, hydration, mist oxygen, and intensive care monitoring for signs of worsening airway obstruction and the need for intubation or tracheostomy.

Neonatal and Pediatric Respiratory Care Technology

Aerosolized Medications

As in adult respiratory care, techniques of bronchopulmonary hygiene are commonly used in

the care of neonatal and pediatric patients, including aerosol therapy and chest physiotherapy (CPT). Although similarities in the treatment of children and adults exist, there are differences as well. Mist-tent therapy is one example of a treatment used in children that is almost never used in adults.

Aerosolized bronchodilators are commonly used in children with asthma[113-120] and have also been shown to be beneficial in children with BPD.[121] These aerosols can be administered by small-volume nebulizer, metered dose inhaler (MDI), or dry powder inhaler. In children less than 5 years of age, small-volume nebulizers are most commonly used, although the use of MDI with auxiliary spacer device has been described.[122,123] Many children over 5 years of age can use an MDI correctly. In those children who cannot use an MDI effectively, a spacer device can be used.[124-126] Dry-powder inhalers have only recently become available in the United States, and few data are available regarding their usefulness.

Beta$_2$-agonists, anticholinergics, cromolyn sodium, and steroids have all been reported to be of benefit in treating children with reactive airways disease.[127-133] One of the greatest differences between the use of these medications in children (particularly infants) and adults is related to dosage. Although appropriate dosages of these drugs are well known for adults, appropriate dosages have not been established for infants.[134] In children with acute asthma, frequent or continuous beta-agonist therapy has been recommended.[135-139] Some children with asthma also use aerosolized bronchodilators at home,[140,141] although some authors have expressed concern that this may result in delayed recognition of the need for medical assistance during acute exacerbations.

Several aerosolized medications are used more commonly in infants and children than they are in adults. For example, aerosolized ribavirin is used to treat children with RSV.[142-144] This therapy requires the use of a specialized nebulizer, the small particle aerosol generator (SPAG).[145,146] Ribavirin can be administered via hood, tent, face mask, or mechanical ventilation.[147] The use of ribavirin aerosol in elderly volunteers at risk for influenza has also been described,[148] but is not currently recommended. Considerable controversy exists regarding the use of ribavirin, including determination of the appropriate patients to be treated with ribavirin and the effects of ribavirin exposure on the health-care provider.[149] Aerosolized antibiotics are occasionally used in the treatment of *Pseudomonas aeruginosa* infections in children with cystic fibrosis;[150-153] however, appropriate dosage and treatment frequency are uncertain at this time. Aerosolized amiloride, a diuretic and sodium-channel blocker, has been shown to enhance mucus clearance in patients with cystic fibrosis and has potential as a mucolytic agent in these patients.[154,155]

Bronchopulmonary Hygiene

CPT is commonly used in children with CF,[156] although for this purpose its usefulness has been questioned.[157] CPT has been reported to be beneficial in neonates: Finer and Boyd[158] reported improvement in oxygenation following CPT, Etches and Scott [15] reported increased secretion removal following CPT, and Finer et al[160] reported a lower incidence of postextubation atelectasis in infants receiving CPT. However, the use of routine CPT in premature infants with RDS is controversial, particularly because many of these babies do not have excessive secretions and because handling of these babies can result in hypoxemia.

Several forms of therapy have been described as alternatives or supplements to CPT in the treatment of CF. These include use of a positive expiratory pressure (PEP) mask,[161-167] autogenic drainage,[168] forced expiration technique (FET),[169] and chest-wall oscillation.[170-174] PEP-mask therapy involves expiration against a fixed resistance, so that positive pressure remains in the lungs at end-exhalation. It has been suggested that this may improve collateral ventilation and in that way aid in the removal of secretions. Several studies [161-163] have reported significantly greater sputum expectoration with PEP than with CPT. However, others have found no difference in sputum elimination between the two therapies,[164] and more sputum expectoration with CPT than with PEP.[165] Autogenic drainage is a technique designed to produce the highest possible airflow in different generations of bronchi by a three-phase controlled-breathing program.[168] FET consists of one or two huffs (forced expirations from midlung volume to low lung

volume), followed by a period of diaphragmatic breathing.[169] Chest-wall oscillation, using a Pneumoband or vibrating pad that encircles the chest wall, has also been described as a technique to facilitate mucus clearance.[170-174] The principal advantage of these techniques seems to be that they can be performed by a patient without the assistance of another person. However, they also require considerable patient instruction and motivation. Although these techniques have achieved some popularity in Europe, none is currently used widely in the United States. Clearly, further research is necessary to evaluate these techniques.

Positive-Pressure Breathing

Positive-pressure breathing is commonly used in neonates, children, and adults with respiratory failure. There are several aspects of this therapy that are interesting to compare in relation to adult and pediatric respiratory care, including the use of continuous positive airway pressure (CPAP), pressure-controlled inverse-ratio ventilation (PCIRV), and high-frequency ventilation (HFV). CPAP was described by Gregory et al[175] in 1971 to treat infants with RDS. Since that time, CPAP has been applied to infants by a variety of techniques including the use of nasal prongs, nasal and face masks, hoods, and endotracheal tubes. It is my impression that the popularity of neonatal CPAP has waxed and waned over the past 15 years and that its current popularity may be attributed to reports [176-179] of lower BPD incidence in centers where CPAP is used to minimize the need for mechanical ventilation. In these reports it has been suggested that the risk of BPD can be decreased by allowing P_{aCO_2} to rise above the physiologic range in low-birthweight infants. Although CPAP is also useful in some adults with acute respiratory failure who are not intubated,[180] this therapy is not commonly used. It has recently been shown that nasal-mask CPAP may be useful for treating some adults with respiratory failure,[181-184] and nasal-mask ventilation has been successfully used in adults in some centers.[185-189] Although the use of positive pressure in nonintubated adults is now recognized as a viable treatment modality, it seems to me that neonatal-respiratory-care clinicians have been (and perhaps still may be) ahead of adult-care clinicians with this therapy.

Virtually all neonatal mechanical ventilators use some form of pressure-controlled ventilation, rather than the volume-controlled ventilation used with adults. In the early 1970s, Reynolds et al[190-193] showed that limiting the pressure during the inspiratory phase of neonatal ventilation decreased the risk of barotrauma and BPD. They also advocated the use of prolonged inspiratory times, with the use of inverse I-E ratios if needed to maintain oxygenation. It is unclear whether Reynolds et al appreciated the role of auto-PEEP during this form of ventilation, but others recognized the relationship between mean airway pressure, oxygenation, and barotrauma. I believe that neonatal-respiratory-care practitioners probably appreciated the mechanical and physiologic effects of mean airway pressure before their adult-care colleagues.[194,195] It is interesting to note that although the use of prolonged inspiratory times and inverse-ratio ventilation seems to have become less popular for neonatal mechanical ventilation, it has recently been advocated for the treatment of ARDS.[196-199] However, use of this method of ventilation in the treatment of ARDS has been criticized,[200-202] and its future role in adult mechanical ventilation is unclear.

Considerable interest in the use of HFV was seen in the early-to-mid 1980s, and this subject has been exhaustively reviewed elsewhere.[203-207] In adult respiratory care, interest in HFV seems to have decreased, particularly because randomized clinical trials have failed to show HFV to be clearly superior to conventional ventilation (CMV) in the treatment of patients with ARDS.[208-210] The current role of HFV in adults is unclear. Several commercially available neonatal ventilators are capable of providing HFV. It has been shown in neonates with RDS that HFV can maintain pulmonary gas exchange comparable to that maintained by CMV, but at lower mean airway pressures.[211,212] Theoretically, the ability of HFV to maintain adequate gas exchange at lower mean airway pressures should decrease the risks of barotrauma and BPD. However, a multicenter randomized clinical trial that compared CMV to high-frequency oscillatory ventilation (HFOV) in preterm infants with respiratory failure found no difference in survival or incidence of BPD between the two forms of ventilation.[213,214] Furthermore, this trial found that

HFOV may be associated with undesirable side effects such as intracranial hemorrhage.

Monitoring

Continuous noninvasive monitoring of respiratory function has been used for many years in neonatal ICUs. Transcutaneous monitoring of P_{O_2} has been commonly used with neonates since the mid-1970s, and transcutaneous monitoring of P_{CO_2} has been commonly used since the early 1980s.[215-217] Impedance apnea monitoring is also commonly used in neonates. Noninvasive monitoring of adults was not commonly used until the introduction of pulse oximetry in the mid-1980s. Although pulse oximetry is now commonly used with neonates,[218-223] it has been criticized because of its inability to detect hyperoxemia.[224]

Extracorporeal Membrane Oxygenation

In the early 1970s, there was initial enthusiasm for the use of extracorporeal membrane oxygenation (ECMO) in the treatment of adult acute respiratory failure. However, ECMO was virtually abandoned in the care of such adult patients following the National Institutes of Health (NIH) ECMO trial,[225] in which it was found that the survival of patients treated with conventional mechanical ventilation (8.3%) was not different from the survival of patients treated with ECMO (9.5%). In this study, however, ECMO was used to supplement mechanical ventilation, and thus the lung was not allowed to rest during ECMO. In the 1980s, Gattinoni et al described a technique of low-frequency positive-pressure ventilation with extracorporeal CO_2 removal (LFPPV-ECCO$_2$R).[226-228] During LFPPV-ECCO$_2$R (Fig. 7), CO_2 is removed by a low-blood-flow (25-30% of the cardiac output) venovenous extracorporeal circulation. Arterial oxygenation is achieved through the natural lung using a variant of apneic oxygenation. LFPPV-ECCO$_2$R allows the lung to rest by limiting the respiratory rate to 2-4/min and limiting peak pressures to 35-45 cm H_2O (3.4-4.4 kPa). High survival rates have been reported using LFPPV-ECCO$_2$R in nonrandomized, uncontrolled applications to ARDS patients.[226] However, until controlled studies are completed, it is premature to recommend the use of LFPPV-ECCO$_2$R in adult patients with acute respiratory failure.[229]

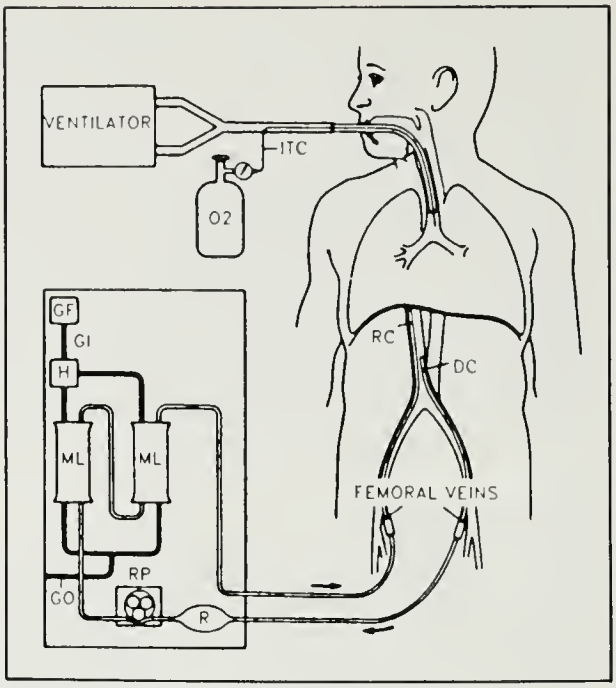

Fig. 7. Configuration of a system for patient support with low-flow positive-pressure ventilation and extracorporeal CO_2 removal (LFPPV-ECCO$_2$R). (Reprinted, with permission, from Reference 229.)

Neonatal ECMO has been popularized in specialized neonatal units equipped to perform this procedure, primarily as the result of the efforts of Bartlett et al.[230-239] Neonatal ECMO is designed to allow the lungs to rest. The technique uses cardiopulmonary bypass to provide gas exchange (Fig. 8), and has been described in detail elsewhere. In brief, catheters are passed into the right common carotid artery and right internal jugular vein to the right atrium (venoarterial bypass). A roller pump moves blood from the venous circulation through a membrane oxygenator and then back into the arterial circulation. To prevent clot formation, the technique requires anticoagulation. In 1988, data from a central neonatal ECMO registry were reported that summarized the first 715 cases from 18 centers.[240] Of the 715 patients, 81% survived. The most common diagnoses of these patients were meconium aspiration (310 patients, 91% survived), respiratory distress syndrome (96 patients, 78% survived), diaphragmatic hernia (121 patients, 65% survived), and sepsis (64

patients, 72% survived). The first randomized trial of neonatal ECMO[241] has been criticized because of its statistical approach.[242] However, another more credible randomized trial[243] reported a survival of 97% in ECMO-treated babies vs a survival of 60% in babies treated conventionally.

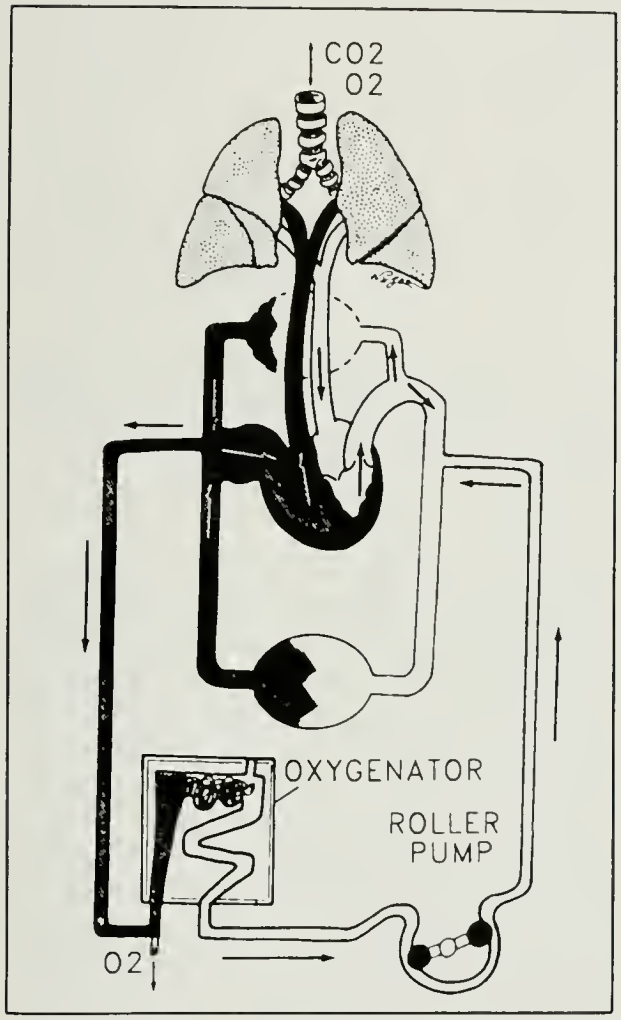

Fig. 8. Configuration of a venoarterial extracorporeal membrane oxygenation (ECMO) system that utilizes cardiopulmonary bypass to rest the lungs. (Reprinted, with permission, from Reference 229.)

Surfactant Administration

Because surfactant deficiency is central in the pathophysiology of infant RDS, it is reasonable to expect that surfactant administration might be useful in the treatment of this disease. However, initial attempts to use surfactant replacement therapy in the treatment of infant RDS were unsuccessful,[244] either because of the surfactant preparation that was used, or because the preparation was aerosolized rather than instilled.[245] In 1980, Fujiwara et al[246] first described the successful use of exogenous surfactant in the treatment of RDS. In the 1980s, many published papers described the use of surfactant in the treatment of RDS,[247-253] and the subject has been reviewed in detail elsewhere.[254-267] A synthetic lung surfactant for neonatal use has been approved by the Food and Drug Administration (FDA) and is commercially available (Exosurf, Burroughs Wellcome Co, Research Triangle Park NC). Surfactant can be administered at birth (preventive therapy) or after the development of RDS (rescue therapy) and as single or multiple administrations. The results thus far from the investigational use of surfactant to treat RDS in infants suggest that there is an improvement in oxygenation, a reduction in ventilator pressures, a reduction in mortality, a reduction in intraventricular hemorrhages, and possibly some reduction in BPD among survivors.

There are also surfactant changes in ARDS.[268-271] Many of the constituents of permeability pulmonary edema (ARDS), such as plasma proteins, are capable of biophysical inhibition of alveolar surfactant. In ARDS, there may also be a decrease in the production of surfactant by alveolar Type II cells. For these reasons, there is interest in the use of surfactant in the treatment of ARDS. Richman et al[272] instilled surfactant in three patients with ARDS and found a transient increase in P_{aO_2} in two patients and longer benefit in the third. Lachmann[273] also reported initial success with the instillation of surfactant in one patient. Several animal studies[274,275] have suggested that exogenous surfactant might be useful in the treatment of ARDS. However, Zelter et al[276] were unable to detect acutely beneficial effects of aerosolized artificial surfactant (Exosurf) following oleic-acid injury in sheep. However, it is of interest that Zelter et al did find that surfactant administration provided protection against some of the consequences of repeated lung injury. One of the problems related to surfactant administration in adults is the difficulty in delivering an adequate amount of the drug to the lungs. The volume of surfactant required in adults to achieve a therapeutic effect has been estimated to be as much as 250-300 mL. Delivery of this volume as a bolus is likely to compromise the ARDS patient,

and accumulation requires a long period of time.[277] However, several clinical trials are currently underway using aerosolized surfactant in patients with ARDS.[278-280]

The Relationship between Pediatric Lung Disease and Adult Lung Disease

Some chronic respiratory diseases, such as CF and asthma, are known to progress from childhood into adulthood. What is not clearly known is the effect of childhood respiratory trouble (CRT) on the development of chronic airflow obstruction later in life. It is well established that cigarette smoking is the principal cause of chronic airway obstruction. However, it is commonly believed by health-care providers and the lay public that CRT may also be a contributing factor. As early as 1953, Oswald et al[281] reported that subjects with chronic bronchitis recalled having bronchitis or pneumonia more frequently in childhood than did normal controls. Since then, many studies have evaluated the relationship between CRT and the development of lung disease later in life; however, all of these studies may be flawed because they rely on recall of either the subject or the subject's parents to determine the existence of CRT. The relationship between CRT and chronic airflow obstruction in adulthood has been comprehensively reviewed elsewhere.[282,283]

Several papers exploring the relationship between CRT and adult obstructive airway disease have come from the Tucson Epidemiological Study of Airways Obstructive Diseases.[284-288] In the first of these, 1,826 subjects were asked to respond to the question, "Did you have any respiratory trouble before age 5?"[284] Of these 1,826 subjects, 413 reported CRT. Progression of respiratory symptoms and disease differed for those with CRT and was affected by host age and smoking history (Table 3 and Fig. 8). Further work by this group showed similar results even when known asthmatics were excluded.[286]

Several studies[287-292] have evaluated the long-term effects of bronchiolitis (Table 4). In these studies, children previously hospitalized with bronchiolitis were found to have an increased frequency of pulmonary function abnormalities on later follow-up evaluation. These findings suggest that bronchiolitis impairs small airways function and increases bronchial reactivity; however, none of these studies evaluated the effects of bronchiolitis on the tendency to develop obstructive lung disease in adulthood. Clearly, further work is necessary to evaluate the effect, if any, of childhood bronchiolitis on the development of adult obstructive lung disease.

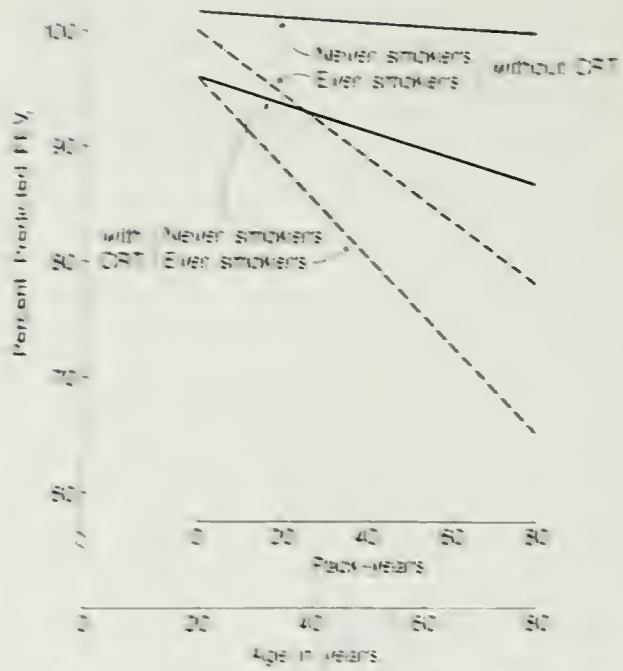

Fig. 8. Regression of percent predicted FEV_1 against age for never smokers and against pack-years for smokers. Reprinted, with permission, from Reference 284.

Other studies[293-296] have evaluated the sequelae of other CRTs (Table 5) and have found a relationship among childhood pneumonia and croup and abnormal respiratory findings at follow-up. Again, further work is necessary to determine whether these CRTs result in the development of adult obstructive lung disease.

The relationship between parental smoking and the development of CRT has been evaluated in several studies.[297-299] Episodes of bronchitis, pneumonia, wheezing, and laryngitis occur more frequently in children of parents who smoke than in children of nonsmokers, and there seems to be a greater effect in the first year of life. Children whose parents smoke have slightly decreased pulmonary function compared to children whose parents do not smoke. Chronic respiratory symptoms

Table 3. Comparison of Prevalence of Respiratory Symptoms and Disease between Adult Individuals with and without a History of Childhood Respiratory Trouble (CRT)*

	Age 20–44 y		Age 45+	
	With CRT	Without CRT	With CRT	Without CRT
	n = 221	n = 822	n = 194	n = 1,389
Symptoms/Disease	(%)	(%)	(%)	(%)
Cough and sputum	36.2	24.2	49.0	35.6
Dyspnea	31.7	22.4	56.2	42.5
Wheezing	43	13.7	46.9	19.8
MD-confirmed pneumonia	43.9	14.6	66.5	27.2
MD-confirmed COPD	5.9	1.9	30.9	11.9
FEV$_1$ < 74% predicted	8.9	4.7	28.9	15.5

*Adapted, with permission, from Reference 284

Table 4. Long-Term Functional Sequelae of Children Hospitalized with Bronchiolitis*

Authors	Sample Size (n)	Follow-Up Interval	Abnormal Findings
Wohl et al[287]	7	≥ 2 mo	2/7 with increased inspiratory & expiratory resistance at 2 mo
Stokes et al[288]	22	13 mo	Hyperinflation and increased resistance in 7/13 children
Kattan et al[286]	23	10 y	Increased RV TLC in 9/22, decreased P_{aO_2} in 1/23
Sims et al[289]	49	8 y	Decreased PEFR, increased exercise-induced bronchial lability
Gurwitz et al[29]	48	9–10 y	20/48 increased RV TLC, 27/48 positive methacholine challenge
Pullan et al[290]	130	10 y	Decreased FEV$_1$ and FVC and increased bronchial lability

*Adapted, with permission, from Reference 282.

such as cough are more frequent in children whose parents smoke. The effects of passive smoking on the respiratory health of children seems to be greater with maternal smoking than with paternal smoking. Maternal smoking has been associated with an increased risk of hospitalization for RSV infection in the first year of life. Although both cross-sectional and longitudinal studies have found that smoking by one or both parents can affect the respiratory health of children, it is not yet known how this

Table 5. Long-Term Functional Sequelae of Pneumonia and Croup*

Authors—Study Population	Sample Size	Follow-Up Interval	Abnormal Findings
Mok et al[293]—children 0.4-11.3 y of age hospitalized with *M pneumoniae*	n = 50	Age 1.5-9.5 y	Abnormal He/O_2 flow-volume curve in nonasthmatics
Loughlin et al[294]—children with MD-diagnosed croup (community)	n = 27	Mean age 11.4 y	Increased exercise-induced bronchial lability
Gurwitz et al[295]—children hospitalized with croup	n = 110	Age 9 y	Increased RV and RV/TLC, positive histamine challenge in 21%
Weiss et al[297]—parental report of croup or bronchiolitis age 5-9 y	n = 194	Age 12-16 y at evaluation	Children with croup or bronchiolitis twice as likely to have bronchial responsiveness to cold air
Voter et al[298]—boys with MD-diagnosed history of lower respiratory illness before age 6 y	n = 57	Age 11-22 y at evaluation	Boys with two or more episodes of wheezing before age 6 had lower levels of performance on spirometry, but no increase in methacholine responsiveness

*Adapted, with permission, from Reference 282.

may affect the probability of developing obstructive lung disease later in life.

The Perinatal-Pediatric Respiratory Care Examination

In March 1991, the NBRC offered the first Perinatal-Pediatric Respiratory Care specialty examination.[310-312] This is the first specialty examination offered by the NBRC, and it recognizes the specialized knowledge required by perinatal and pediatric respiratory-care practitioners. Consideration of this specialty examination began with a viability study in 1985. In 1987, a personnel survey indicated that approximately 12,000 respiratory care practitioners practice in this specialty area. In 1988, a national job analysis study was done, which resulted in an examination matrix. In 1989, the NBRC Board of Trustees voted to implement the examination. Each perinatal-pediatric respiratory care examination will consist of 100 multiple-choice items, and the examination will be given in March of each year. Admission criteria require that applicants be either Certified Respiratory Therapy Technicians (CRTTs) with a minimum of 1 year of clinical experience in perinatal-pediatric respiratory care or Registered Respiratory Therapists (RRTs). The CRTT-clinical experience admission qualification expires 5 years from the date of the application deadline for the first examination administration and will be reviewed after 3 years by the NBRC Board of Trustees. It remains to be seen what impact this specialty examination will have on the practice of perinatal-pediatric respiratory care.

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Hess Discussion

Hess: It would be fun for me and for other respiratory care practitioners to hear some of your thoughts—neonatologists, pediatricians, and pediatric respiratory care practitioners.

Fanaroff: I thought that was a great overview. You know, we have observed a pendulum with regards to terminology—hyaline membrane disease (HMD) became idiopathic respiratory distress syndrome (IRDS), but now that the etiology is known, the I should be dropped. It's no longer idiopathic. Although some retain the I for infant (infant respiratory distress syndrome) to contrast with adult respiratory distress syndrome, or ARDS, RDS does appear to be the usual terminology. You described the condition as surfactant deficiency, and probably throughout these proceedings that is the term that should be used—RDS-surfactant deficiency.

Hess: I appreciate your advice. I wrestled with terminology as I put the paper together—wanting to be sure to make it clear. Thank you.

O'Rourke: One other difference to consider when contrasting adult and pediatric care is that in pediatrics we cannot depend on patient cooperation. If we could calm children down verbally, rather than having to pharmacologically induce cooperation (or paralysis), I think we could avoid intubating a number of children. For example, epiglottitis in children is routinely supported with an endotracheal tube; in adults an artificial airway is often not required.

Hess: That's a very good point.

Orenstein: Another follow-up point on that, which doesn't so much have to do with the difference between kids and adults, but it was eye-opening to me. For the past two decades, we've taught in this country that epiglottitis in children needs to be taken care of in an ICU with an artificial airway. Yet, I observed on a visit to Australia that, in one of their excellent children's hospitals, very few of their children with epiglottitis are intubated—certainly not automatically the way we do here. Their outcome is excellent. So some of what we hand down as absolute truth 'ain't necessarily so.' I think Pearl's (O'Rourke) point is that maybe the differences between kids and adults are more who the people are than what their diseases are. I think we see differences in geography and how diseases are handled but very similar outcomes.

Hess: Very interesting perspective on that. Richard (Martin), do you have anything to add?

Martin: I want to emphasize the new information available on lung growth and ask Alan Jobe to update us.

Jobe: There is some recent information on lung growth in the developing human. Hislop et al[1] and Langston et al[2] have reported that alveoli can be identified in the fetal lung and perhaps 100 million alveoli are present at term birth. This is about one third the number of alveoli in the adult lung. The adult number of alveoli are probably present by 6 months to 1 year of age. Therefore, subsequent lung growth is an increase in alveolar size and not number. This is important information because the period of interest from viability to a year of life encapsulates the process of alveolarization, a process that can be influenced by a number of factors such as oxygen, injury, nutrition, and steroid use.

1. Hislop AA, Wigglesworth JS, Desai K. Alveolar development in the human fetus and infant. Early Human Development 1986;13:1-11.
2. Langston C, Kida K, Reed M, Thurlbeck WM. Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 1984;129:607-613.

Hess: That's a good point. In my paper I do talk about some of Thurlbeck's work.[1] He really does take a lot of that old data and some of the things we commonly see in textbooks to task. The other thing that I think Thurlbeck and others have pointed out[2,3] is that there's a lot of variability from individual to individual that wasn't appreciated at all in some of the earlier work.

1. Thurlbeck WM. Postnatal growth and development of the lung. Am Rev Respir Dis 1975;111:803-844.
2. Langston C, Kida K, Reed M, Thurlbeck WM. Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 1984;129:607-613.
3. Thurlbeck WM, Angus GE. Growth and aging of the normal human lung. Chest 1975;67:35-75.

Stark: I would just like to follow up on your comment about using or not using inverse I:E. I think that what has happened over the last 10 or 15 years is that instead of saying all babies should be ventilated the same way, we have begun paying much more attention to the disease process and to adapting a strategy of ventilation for that particular infant at that particular point in his disease. I think that's important to keep in mind.

Hess: Good point.

Chatburn: Dean, I know that you have been involved in helping to develop the perinatal-pediatric specialty exam. How would you respond to the question by persons who plan to take this exam (who qualify to take it, but have most of their experience in adult clinical care), how do we study to take this exam? How do we prepare ourselves?

Hess: In my opinion, and Patty (Koff) may have something to say about that—she has had a lot to do with the development of this exam. In my opinion, the best way to get ready for that exam is to work in neonatal and pediatric respiratory care. And, it really may not be appropriate at all for people who work in adult respiratory care to take this exam just so they can have another credential or another certificate to hang on the wall. You and I have talked about that before; I think this is an exam that one doesn't prepare for by reading books and spending time in the library. One prepares for this exam by working with neonatal and pediatric patients. Patty (Koff), do you have anything to add?

Koff: The only thing I'd add is that those who work only in a neonatal unit or only in pediatrics are also going to be missing some things because the exam covers both neonatal and pediatric topics. I think regardless of where they're working, they are going to have to put some time in on that other half—the opposite end. If a practitioner only works the PICU and has never worked NICU, he will need some experience in the NICU, and at least is going to have to hit the books. I do think the exam is a broad representation of what the skills are within that subspecialty of the profession.

Hess: Rob, what do you tell people who ask you that question?

Chatburn: Well, those who have had very little actual pediatric and neonatal experience I tell to forget it. For those who do have some experience (particularly those who feel they have a lot of experience), I tell them that the best way to become familiar with taking the test is probably to work in study groups. Ask each other questions or maybe try to simulate creating the exam themselves; so they can focus in on what they really do know and what is mostly conjecture.

Pierson: Rob's question leads very nicely into mine, which is also about the exam and relates to manpower. We spoke of the maturation of the field and the specialization of a large segment of the respiratory care practitioner population in pediatric-neonatal areas. My question is, Do we know how many hospitals have therapists who work only in neonatal and pediatric units?

Hess: I don't know the answer to that. I would defer maybe to Patty Koff or to Sam Giordano who might have some idea from the AARC job surveys.

Giordano: When we do manpower or human resources surveys, we do ask that job titles be made known to us. The perinatal-pediatrics specialist title did not come up as one of the top five when we performed our last human resource survey in 1986.

However, we are presently designing a RCP census—it's a little different from a human resources survey—to be conducted in all job settings. From that survey, we will know how many perinatal-pediatric specialists exist and in what institutions they work—in terms of hospital size and geography.

Hess: Part of the reason for not being one of the "top five," Sam, may be that in some hospitals a group of therapists may work only in the neonatal ICU but they don't have a special title. They are just called respiratory therapists, and their assignment is that each day they report to the NICU.

Pierson: The reason for my asking is that I wonder if this group wouldn't agree that perhaps the standard in the profession, in a hospital of sufficient size, should be dedicated specialized practitioners—especially for neonatal ICUs.

Salyer: First, I generally agree with Dr Pierson with regard to dedicated NICU specialists, except that practically speaking we may be 'shooting ourselves in the foot' in terms of efficient utilization of manpower by doing that. I guess I want to go on record because we are talking about the NBRC exam by saying how unfortunate I think it is that the NBRC has chosen not to attach 'initials' to this examination. As far as I know (although someone may correct me), this is the first examination conducted by the NBRC for which successful participants have not been recognized by an identifiable title (eg, RRT, RPFT). Initially, the participation in this examination process had great, broad support in our hospital, but interest has somewhat dwindled. Some of that loss of interest and support has resulted from our learning that a specific credential designation will not be awarded to those therapists who have 'paid the price' for taking the exam and have successfully completed it.

Barnes: I have been pleased to see graduates of our baccalaureate program provide leadership at Boston's Children's Hospital in ECMO and clinical research. In my opinion, the profession needs to encourage more schools to move to a minimum of 2 years of education and increase the number of 4-year programs beyond the 25 currently operating.

Delivery of Aerosolized Drugs to Neonatal and Pediatric Patients

Joseph L Rau Jr PhD RRT

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- Summary and Conclusions

CONCLUSIONS

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INTRODUCTION

This review focuses on the effectiveness of aerosol drug delivery in neonatal and pediatric patients. In considering the question of effectiveness, I believe that a systems approach helps to clarify the number of interacting variables that ultimately determine the outcome of the drug treatment. Each of the components shown in Figure 1 has a major influence on any conclusion regarding the effect of aerosolized drug treatment in this population:

—the measurement system used to determine effect;
—the pharmacotherapy of the developing lung;
—the aerosol delivery system employed;
—the clinical effect of the agents used.

A systems approach serves to emphasize that results must be interpreted with the realization that each component of the system interacts with the others and can alter the conclusions drawn. The drug must be suited to the pathophysiology of the patient; the particle size generated and the delivery system must be suitable to reach the targeted area of the lung or airway; and the measurement of the drug effect must be sufficiently sensitive, accurate, and precise to detect change. First, I present a cursory overview of pulmonary function measuring systems to identify the techniques on which cited results are based. Then, in the second section, I highlight major aspects of neonatal-pediatric pharmacology that favor aerosol administration of drugs. The third and major part of the discussion centers on aerosol delivery systems in neonates, infants, and children, and the final section on the efficacy of each class of drugs used in this population. Discussion of the use of aerosolized antibiotics in cystic fibrosis and of exogenous surfactant treatment is left for other presentations in this symposium.[1,2]

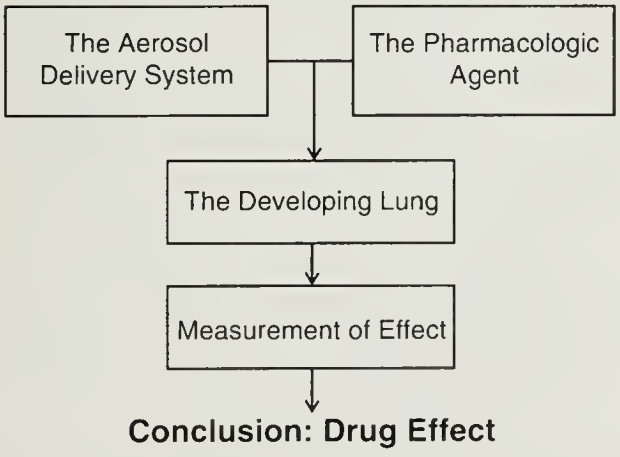

Fig. 1. Results of evaluation of the four interacting components shown affect conclusions regarding the efficacy of aerosol delivery.

Abbreviations Used in This Paper

BPD	— Bronchopulmonary dysplasia
DPI	— Dry powder inhaler
ETT	— Endotracheal tube
$FEF_{25-75\%}$	— Forced expiratory flow between 25% and 75% of vital capacity
FEV_1	— Forced expiratory volume in one second
FRC	— Functional residual capacity
MDI	— Metered-dose inhaler
MMAD	— Mass median aerodynamic diameter
PEFR	— Peak expiratory flowrate
PIFR	— Peak inspiratory flowrate
RSV	— Respiratory syncytial virus
SVN	— Small volume nebulizer
Vd	— Volume distribution
$\dot{V}_{maxFRC}$	— Maximal expiratory flow at FRC

MEASUREMENT OF PULMONARY FUNCTION IN NEONATAL AND PEDIATRIC PATIENTS

These various methods of measuring pulmonary function are cited in the literature on aerosol delivery systems and the efficacy of various drug classes, and are themselves variables. The measurement of the effects of aerosolized drugs on the lung has gradually evolved from the measurement of forced breaths (such as that used with adults) to a form of continous monitoring of pulmonary mechanics

on a breath-by-breath basis using computer-based systems. Such systems are exemplified by the Med-Science RDS 4500, the Infrasonics StarCalc, and the SensorMedics 2600, all dating from 1988. A conceptual schematic of a generic computer-based pulmonary monitoring system for infants is given in Figure 2. Although these systems display values

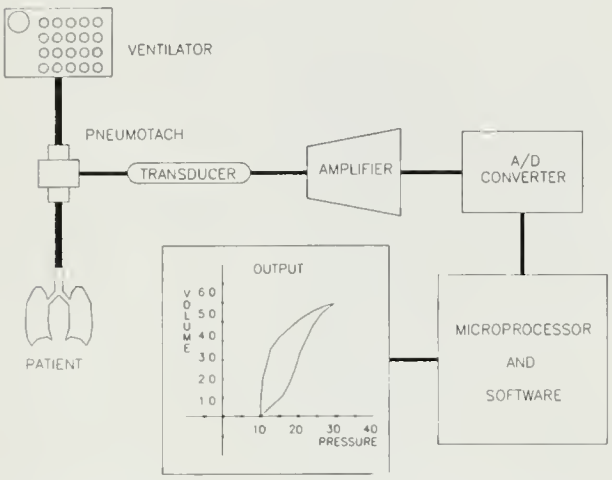

Fig. 2. Major components of a computer-based pulmonary monitoring system.

for 25 or more variables, all the values ultimately derive from pressure differences sensed by the pneumotachograph. This measurement of pressure differences is translated into flow, based on known pressure-flow-resistance relationships. Volume is derived by integrating flow over measured time. The software of the system then 'massages' the primary pressure and time measures into the numerous derived variables provided. In my opinion, the operation of these 'black box' systems is probably easier than the evaluation of their validity or the interpretation of their meaning for clinical decision making. Milner[3] provides an excellent overview of lung function testing methods for infants, and the interested reader is referred to his review article. The methods encountered in the literature to measure the effects of aerosolized drugs are given in Table 1.[4-14] The gold standard is considered to be body plethysmography.[3] Systems such as the Med-Science and the Infrasonics are based on the esophageal-pressure and mouth-flow principle, with or without actual esophageal pressure measurement. The most commonly used methods of evaluating lung function changes associated with the delivery of aerosolized drugs are the pressure-flow method, body plethysmography, forced partial expiratory flows, and some variation of the weighted spirometer technique.

Table 1. Techniques of Measurement for Pulmonary Function Evaluation in Infants and Small Children

Esophageal pressure and airway flow[4,5]
Total body plethysmography[6]
Weighted spirometry[7]
Closed-circuit lung volumes[8]
Single-breath pulmonary mechanics[9]
Forced partial expiratory flow-volume or deflation flow-volume[10-12]
Forced oscillation[13,14]

PHARMACOTHERAPY OF THE DEVELOPING LUNG

Drug pharmacokinetics and pharmacodynamics are markedly altered in neonates and infants and, to a lesser extent, in children. This fact argues in favor of a topical, inhalational administration of aerosolized drugs, especially for pulmonary diseases, despite the problems associated with imprecise aerosol delivery. I want to identify and briefly comment on those factors of neonatal/pediatric pharmacotherapy that favor aerosol delivery. Reviews of general pharmacology for this age group are well beyond the scope of this review and can be found in other sources.[15-18]

The following terms are defined in accord with general use, although variation exists in the literature for definition of premature.[15,18-21]

premature—less than 38 weeks gestational age
full gestational age—38 through 42 weeks
neonate—birth to one month
infant—1 through 12 months
child—1 through 12 years
adolescent—13 through 17 years

Table 2 lists the advantages of aerosol delivery in the treatment of lung disease. The general advantages of aerosol therapy shared with adults are not discussed. Certain advantages, however,

derive from the age range and from the altered pharmacokinetics and pharmacodynamics of this age group.

Table 2. Characteristics that Favor Drug Delivery by Aerosol to Infants and Children

Localized treatment of target organ
Safe, painless, and convenient route
Rapid onset of drug effect
Lower dose requirement than with oral administration
Reduction in number and severity of side effects
More practical than oral administration
Avoids problems associated with systemic routes in neonates
—lack of an ideal dosing rule
—variable gastric emptying time
—decreased gastrointestinal transit time
—increased gastric pH
—altered volume of distribution
—altered bound drug fractions
—altered pancreatic enzyme status
—altered gastrointestinal flora

Lack of an Ideal Dosing Rule

Short of expensively and invasively monitoring blood and organ levels of a drug, no ideal method of estimating drug doses for neonates, infants, and children exists. Empirical formulas based on weight, height, age, or body surface area are often used. Body surface area is said to correlate better than do the other variables with physiologic factors that affect drug action.[22,23] These formulas are linear proportions and fail to account for nonproportional differences between adults and infants. Differences include missing enzyme systems, variables of gastrointestinal absorption, and altered volumes of distribution. Pharmacodynamics with changing or immature receptor response is also variable.[24] Local topical administration of aerosols by inhalation can bypass the need to use estimates based on body size and, also, the pharmacokinetic and pharmacodynamic problems of systemic therapy.

Practicality of Inhalation

Neonates, infants, and very young children are unable to follow directions or explanations. This is coupled with drooling, spitting, and the tendency to expectorate unpleasant tasting oral medications. Instillation of eye, ear, or nose drops, injections, starting an intravenous line, and insertion of suppositories can be traumatic for both the young patient and the practitioner. Coupling drug delivery with the act of breathing offers a convenient route of drug administration with minimal discomfort or need for direction.

Gastric pH

Gastric pH ranges from 6 to 8 at birth, and falls to about 1.5 within hours, but does not approach adult values until approximately 3 months of age.[25] In general, gastric pH in neonates and infants is higher than in adults.[15] Acid secretion also tends to be less with parenteral than with enteral nutrition. Because drug absorption from the stomach is partially dependent on the ambient pH and pKa of the drug, gastric pH affects the bioavailability of orally administered drugs.[25]

Gastric Emptying and Transit Times

Two characteristics of the gastrointestinal tract can affect drug absorption and bioavailability in neonates, infants, and children. First, gastric emptying times may be slower in neonates and infants than in adults. Prolonged gastric emptying time delays the peak concentration of oral medication that is absorbed primarily from the intestines.[25] Factors including prematurity, respiratory distress syndrome, and congenital heart disease may further decrease rates of gastric emptying.[26] Secondly, the transit rate through the intestinal tract is usually increased in infants and young children.[15] Sustained or slow-release products such as theophylline may move through the intestinal tract before they have time to be absorbed from the optimum region of the proximal small intestine.[27] In particular, feedings can further increase transit rate so that drugs mixed with food (eg, sprinkled beads) can end up in the diaper with little or no absorption having occurred.[15,28]

Volume of Distribution

Another factor directly affecting the pharmacokinetics of a drug is the subject's apparent

volume of distribution, or Vd. The Vd is the storage compartment in the body that determines the concentration of drug in the plasma. The Vd in turn is affected by the percentage of body water, which is higher in neonates, infants, and children than in adults.[25,29] Other age-dependent factors such as protein binding also affect the Vd. As a result, the concentration of a water-soluble drug on a milligram/kilogram of body-weight basis, is less for neonates and infants than for adults, given the increased percentage of body water.

Bound Fraction of a Drug

In general, the unbound portion of a drug in the bloodstream is the active portion. A number of age-related factors affect drug binding to plasma proteins: the concentration of such proteins, the number of binding sites, the affinity of drug and protein, and the influence of competing substances and pathophysiology. As a specific example, theophylline is approximately 36% bound in the child and infant, but 52-65% bound in the adult.[30,31]

Pancreatic Function

Relative pancreatic insufficiency is present at birth, and pancreatic enzyme activity is lower in premature than in full-term infants.[25,32] Drugs such as chloramphenicol that require hydrolysis in order to be absorbed have reduced bioavailability, and dosage schedules need to be adjusted upward.

Gastrointestinal Bacteria

The composition and presence of bacterial flora in the gastrointestinal tract can influence intestinal motility and the metabolism of drugs.[33] Such colonization varies with postnatal age and with the type of delivery, feeding, and drug therapy.[25,34]

These factors as well as others not mentioned, such as renal function, introduce a tremendous degree of uncertainty and unpredictable variability into systemic drug dosing in the neonatal-pediatric population. Despite the unanswered questions surrounding aerosolized drug therapy, particularly in neonates and infants, avoidance of the systemic route becomes a major motivation for pursuing a topical route of administration.

THE AEROSOL DELIVERY SYSTEM

Drug Doses in Neonates, Infants, and Children

Aerosol therapy is plagued by lack of information on appropriate doses for neonates, infants, and, often, children. Eighteen drugs are currently (1991) approved for aerosol administration if we include the atropine sulfate formulation by Dey Laboratories. With the exception of ribavirin, no neonatal or infant doses for any of these have been established. The package inserts for racemic epinephrine and acetylcysteine do not specify aerosol doses for children or infants, but the use of acetylcysteine in croup tents is discussed. The youngest age specified in dose recommendations is 2 years and above for cromolyn sodium by nebulizer or inhaled powder. Except for inhaled dexamethasone (which specifies "children"), the aerosolized corticosteroids are for children 6 years and above.

Manufacturers do not usually perform studies of clinical efficacy and dose range in infants and children. Dose-response studies are lacking from other sources as well. As a result, dosage schedules for aerosol are usually determined empirically, often based on the subject's body weight. One exception is a study by Nussbaum and associates that determined a dosage of 0.01 mL/kg, of a 5% solution of metaproterenol for 3- to 6-year olds as optimal.[35]

Table 3 lists the most commonly found dosage schedules for aerosolized agents. The doses are taken from the manufacturer's information or based on references, none of which is an actual study.[15,23,36-42] Some variability is seen in the referenced literature. For instance, Dupuis and Spino,[23] in Pagliaro and Pagliaro's text, indicate a dose of 0.1 mL/kg of albuterol, up to a maximum of 1 mL. Unless this is an error, the dose recommended is more than three times higher than other recommendations, and the maximum is twice that used in adults. Kelly's review article[15] gives pediatric doses of drugs to be aerosolized including the injectable solutions of terbutaline (0.1 to 0.3

Table 3. Dosage Guidelines for Nebulized Solutions for Neonates, Infants and Children

Solutions	Dosage
Sympathomimetic bronchodilators	
Racemic epinephrine	0.05 mL/kg of 2.25% solution; not more frequently than q2h maximum dose 0.5 mL
Isoproterenol	0.025 mL of 1:200 solution or 0.01 mL/kg, maximum = 0.05 mL; tid, qid
Isoetharine	0.25-0.5 mL of 1% solution; q4h
Metaproterenol	0.2-0.3 mL of 5% solution; q4h
Albuterol	0.01-0.03 mL/kg of 0.5% solution, maximum = 0.5 mL; tid, qid
Bitolterol	MDI only
Pirbuterol	MDI only
Anticholinergic bronchodilators	
Atropine sulfate	0.05 mg/kg, maximum = 1 mg.
Ipratropium	MDI only (USA)
Mucolytic agent	
Acetylcysteine	3-5 mL of 10 or 20% solution; tid, qid
Corticosteroids	
Dexamethasone	MDI only
Beclomethasone	MDI only
Flunisolide	MDI only
Triamcinolone	MDI only
Antiasthmatics	
Cromolyn sodium	> 2 years, 20 mg qid
Nedocromil	MDI only
Antiinfectives	
Ribavirin	6 g/300 mL (2%), 12-18 h/day
Pentamidine	≥ 5 years, 300 mg/ month by Respirgard*

*JAMA 1991;265:1637-1644.

mg/kg, every 2-6 h), epinephrine, and atropine. A survey of doses used at 71 pediatric centers has been reported in abstract form.[43] Although this information may be helpful, it is one step removed from the real question, What doses, if any, are effective in neonates, infants, and children? Perhaps the lack of information on effective neonatal and pediatric doses is the reason for little or no discussion of aerosol drugs in such texts as Lough et al[44] and Aloan.[45] Koff et al[46] give dosage standards for only sympathomimetic and anticholinergic agents, although they devote a chapter to neonatal and pediatric pharmacology. Even a text such as Yeh,[22] on drug therapy of the neonate, lacks any mention at all of aerosolized delivery or dosage. Based on what is available in the literature, both text and journal articles, aerosol doses for this age group need to be determined by a scientific approach using dose-response curves. A comprehensive approach would factor age levels into such studies to examine the relation of age to dosage. It is surprising that studies of the efficacy of aerosol therapy have often used the accepted doses in Table 3 rather than developing dose-response curves, which could be done within the studies.[47-52]

In theory, a topical treatment such as aerosol therapy should not be based on body size in the way systemic therapy is. If we use schedules based on body size, are we not defeating the very advantage of topical over systemic therapy? Body size may not correlate well with overall development of the body's response systems, as discussed previously. Topical drug administration depends primarily on the presence and development of receptors for its effect. This aspect, the pharmacodynamics of drug therapy, can be examined in controlled dose-response studies. Lower receptor density or immaturity could necessitate stronger doses than those used in adults. The recommended doses of nebulized atropine sulfate suggests this: 0.05 mg/kg for children, but only 0.025 mg/kg for adults.[53]

Variables in the Aerosol Delivery System

In keeping with a systems approach, we can see that any conclusion regarding an aerosolized drug's

effectiveness depends heavily on the delivery system employed. A number of technical details can be varied in configuring a delivery system. Three primary elements, with their possible choices, are listed in Table 4. The number of possible combinations to form a delivery system, although not unrestricted, can explain conflicting or inconsistent research results. In some studies, the details of aerosol delivery have been left to the imagination of the reader. For example, in a study by Steventon and Wilson[54] comparing face mask to mouthpiece delivery with a nebulizer, instructions on breathing pattern are never mentioned, the type of breathing with the mask (nasal or mouth) is not described, and the particular compressor used is never identified. The compressor used has been shown by Newman and co-workers[55,56] to be an important variable affecting aerosol generation and delivery. If results are to be compared and interpreted, editors and reviewers must demand full specification of the aerosol delivery system. Systematic and comprehensive investigation of the effect of the many variables identified in Table 4 is needed.

Table 4. Primary Elements and Their Variables for Aerosol Delivery Systems

Power Source
Self-contained propellants
Manual resuscitator (''bag'')
Ventilator
Flowmeter (ie, high-pressure piped or cylinder gas)
Compressor
Patient (ie, breath-actuated)
Electricity (transducer)
Generator
Metered dose inhaler
Small volume nebulizer
Dry powder inhaler
Large volume nebulizer (SPAG)
Ultrasonic nebulizer
Interface
Mouthpiece
Mask
Spacer device
Endotracheal tube
Oxygen hood or tent

Aerosol Delivery in Spontaneously Breathing Patients:

Three commonly used aerosol generators for drug inhalation are the small-volume, gas-powered, hand-held nebulizer (SVN), the metered dose inhaler (MDI), and the dry powder inhaler (DPI). An MDI can be combined with an extension, or spacer device (also termed an auxiliary delivery system). In my estimation, ultrasonics and nebulizers based on the Babington principle are not commonly used for drug delivery in the United States. The Small Particle Aerosol Generator, or SPAG, is associated exclusively with delivery of ribavirin. Devices such as the AeroTech II (Cadema Medical) and the Respirgard II (Marquest) are modifications of the small-volume nebulizer specifically for anti-infective aerosols.

Table 5. Age Guidelines for Modes of Aerosol Drug Delivery

Mode*	Minimum Age
SVN	neonate
MDI	7 years
—with spacer	3 years
—with spacer and mask	infant
—with ETT	neonate
DPI	3-4 years

*SVN = small volume nebulizer; MDI = metered dose inhaler; ETT = endotracheal tube; DPI = dry powder inhaler.

Guidelines regarding minimum ages for prescribing each of these three modes of aerosolization have been published,[39,57,58] and are summarized in Table 5. Although the most common device for spontaneously breathing infants has been the nebulizer, several studies have reported positive results using an MDI fitted to a spacer, with a soft mask attached.[59-61] Yuksel and colleagues[61] simply adapted an MDI to a coffee cup placed over the face of the infant (median age 12.5 mo, range 25-36 mo). All three studies were of weak design. One study contained no comparison group.[59] A second contained inconsistencies in the data provided and inappropriately used the Fisher exact test for frequencies in a matched-pairs design.[61] The strongest study compared bronchodilator by MDI

to placebo, although a comparison of bronchodilator by nebulizer might have been more informative.[60] These results probably should be considered as preliminary, with further investigation warranted. As with any descriptive guidelines, the response of the individual child or infant determines success with a particular mode or device.

Small Volume Nebulizer

The small volume nebulizer (SVN), profiled in Table 6, has been widely used in hospitals and often at home. The SVN has the major advantages of being able to aerosolize almost any drug available in liquid form and of allowing modification of dose volume and concentration. These features, together with minimal patient-coordination requirements, have made nebulizers attractive for use with infants and young children, usually with a mask attachment. Infants however may fight a mask and try to avoid the cold, damp spray of aerosolized liquid.

Table 6. Advantages and Disadvantages of Small Volume Nebulizers for Aerosol Delivery

Advantages
Little patient coordination required
Useful in very young infants and children
Useful in acute distress (tachypnea) or reduced inspiratory flows and volumes
Allows modification of drug concentration
Allows aerosolization of almost any liquid drug
Effective without breath-holding
Disadvantages
Expensive
Not easily portable
Requires preparation and cleaning
Inefficient dose delivery
Cold, wet spray with mask delivery
Provides medium for bacterial growth

Metered Dose Inhaler

The MDI is unquestionably far more efficient than nebulizer delivery both in terms of dosage delivered and time for use (Table 7). However, it has a major disadvantage of requiring some degree of coordination of hand and inhalation, which makes its use in children, especially under 7 years of age, questionable.[62] Obviously the motor coordination and level of understanding of individual children varies widely and influences success with MDI use. Unfortunately, MDI use may be complicated even further by the lack of knowledge among health care professionals on proper use.[63]

Table 7. Advantages and Disadvantages of Metered Dose Inhalers and Spacer Devices for Aerosol Delivery

Metered Dose Inhalers	
Advantages	**Disadvantages**
Very portable	Difficult hand-breath coordination
Efficient drug delivery	Fixed drug concentrations
	Limited range of drugs available
Short preparation and administration time	Possible reaction to propellants
	Possible high oropharyngeal impaction
	Possible foreign body aspiration from mouthpiece
Spacer Devices	
Advantages	**Disadvantages**
Reduce need for hand-breath coordination	May be large and cumbersome
Reduce oropharyngeal impaction	
Reduce oropharyngeal candidiasis with corticosteroids	

The key elements for optimal MDI use are generally based on Newman et al and Dolovich et al's findings published in 1981:[64-66]

> Shake MDI and discharge once prior to use;
> Position MDI 4 cm in front of wide open mouth;
> Activate MDI at end-exhalation (FRC);
> Inspire slowly;
> Hold the breath 10 seconds at total lung capacity.

The reason for shaking and discharging the MDI prior to use is to thoroughly mix the active drug throughout the chlorofluorocarbon propellant, and to 'charge' the valve assembly. A pause between puffs of a bronchodilator may be helpful during acute bronchospasm but less so for routine maintenance.[67] Instructions to patients contained in the package inserts of MDI devices invariably

illustrate the MDI with the mouth tightly closed around the mouthpiece; this has at least two disadvantages. First, high oropharyngeal impaction results in loss of delivery to the lung and may cause a reflex cessation of inspiration.[68] Secondly, smaller inhaled volumes can result unless the patient opens his mouth during inspiration. The patient may even breathe nasally with the mouth closed on the mouthpiece. However, a good example of the confusion surrounding results of studies on aerosolized drug delivery is provided by the study of Unzeitig and others[69] who found no difference in peak expiratory flowrates (PEFR) between open and closed mouth use of an MDI. Subjects were asthmatic children aged 7 to 16 years. This result is inconsistent with the findings of Dolovich et al and other investigators.[65,70,71] Such inconsistency occurs often with studies of aerosol delivery and underscores the need for careful design and full technical description of aerosol systems. Several important differences exist between the Dolovich et al and the Unzeitig et al studies.[65,69] Dolovich et al did not use a bronchodilator, only a radiolabeled aerosol, and measured deposition, not clinical effect on PEFR. Dolovich et al used a particle size of 2.15 μm mass median aerodynamic diameter (MMAD). The isoetharine MDI (Bronkometer) used by Unzeitig et al produced approximately 5.5 μm particles when measured by Sackner and Kim.[72] Perhaps more telling are potential flaws in Unzeitig et al's study.[69] Oral bronchodilators were not discontinued for the study, which may have created a ceiling effect, and poses a threat to the internal validity of the study. Secondly, the authors state that a "Student unpaired T test" was used, which is incorrect for the crossover design employed. Although this may not lead to a different conclusion from analysis by paired *t* test in this instance, the inappropriate choice is disconcerting. Pending further support of a closed-mouth technique, I recommend positioning the MDI approximately 4 cm in front of the open mouth.

MDI with Spacer Devices

MDI auxiliary delivery systems, or spacer devices, allow time for propellant vaporization to achieve a smaller particle size (particle aging) and reduce excessive oropharyngeal impaction.[72-74] Their use is summarized in Table 7. Spacer devices extend the convenience of using MDIs to more and younger children;[58,75,76] however, questions remain about their use, particularly for children.

What inspiratory flowrate should be used with an MDI-spacer combination? Low flowrates have been suggested to reduce oropharyngeal impaction, and this is supported by data.[72,77-79] Yet, an abstract of a study with a lung model reported higher lung deposition with large-volume spacers (1,350 mL) and high inspiratory flowrates of 60 L/min.[80] In contrast, two clinical studies with children found improved drug response using either "normal" breaths from FRC or slow inspiratory flowrates of 15-30 L/min compared to 70 L/min.[81,82] Unfortunately, as has often been the case with aerosol studies, either lung deposition or clinical response (but not both) was measured in the three studies cited. Is it possible that high inspiratory flowrates could give increased lung deposition, but not improved bronchodilator response? Answering this question requires correlation of clinical response with quantitative deposition.

In a study with adults, Newman and others[74] found that the Nebuhaler spacer could be used with either single MDI puffs or multiple MDI puffs all inhaled at once. With multiple puffs inhaled in a single breath, the lung deposition decreased from approximately 21% to 15%, although oropharyngeal deposition also decreased from 16.5% to 11%.

The effect of the volume of a spacer also warrants investigation in infants and children to resolve these questions. Logic dictates that infants and, in general, subjects with small tidal volumes may not receive the same concentration or total amount of drug from a holding chamber as do adults.[83] Both the size and shape of spacer devices vary widely from 70 mL to 750 mL.[84] One-way valves at the mouthpiece of these devices prevent aerosol from leaking out prior to inhalation. The valves are essential for eliminating the need for MDI activation-inhalation coordination. What effect do these variables have on aerosol delivery with either neonates or small children? Does a pear-shaped spacer (simulating the aerosol cloud from an MDI) make a difference? Can infants open the one-way valve if an MDI-

spacer-mask combination is employed? How many breaths should an infant or child use with spacer devices, and how does this vary with the volume of the device?

Although questions concerning spacer use (particularly with neonates and infants) remain unanswered, the preliminary studies cited indicate the possibility of beneficial clinical results that should be further substantiated.[59-61] For the non-infant group, the consensus is that spacer devices simplify MDI use and reduce oropharyngeal loss.[73,74,85-87] The bronchodilating effect is at least as good as with an optimally used MDI, and better if there is difficulty using an MDI.[88-90] Spacers are recommended when corticosteroids are inhaled with an MDI.[57,91]

Dry Powder Inhalers

The major advantages of both the nebulizer and the MDI are present in the DPI, which consists of a suspension of microfine solid particles of drug, contained in a small, MDI-size device with a mouthpiece. Two drugs are available in this formulation in the United States: cromolyn sodium (Spinhaler Turbo-Inhaler, Fisons) and albuterol (Ventolin Rotacaps and Rotahaler device, Allen & Hanburys). Both use a gelatin capsule containing a micronized powder of the drug and a lactose carrier substance to aid in dispersion of the powder during inhalation. Prior to inhalation, the capsule is pierced or opened by the device to release the contents. New developments with this type of device are emerging. Terbutaline is now marketed in the United Kingdom and Europe as a multiple-dose powder inhaler containing 200 doses (Turbohaler, UK), with no carrier substances such as glucose or lactose.[92] Fenoterol, a beta-adrenergic bronchodilator, is also available in powder form.

Such inhalers offer the convenience of MDI use, but eliminate the need for hand-breath coordination. It has also been shown that head tilting during inspiration and breath-holding afterwards do not significantly add to the efficacy of the DPI.[93] This further simplifies their use. Other advantages and disadvantages are given in Table 8.

Two limitations of DPI devices currently used in this country are the need for high inspiratory flowrates and the need to load and operate the inhaler device. Inspiratory flowrates below 50 L/min have been associated with a significant reduction in clinical response using the Rotahaler.[93,94] During acute asthmatic episodes, children may have peak inspiratory flowrates reduced below this level. In addition, very young children (below 5 years) or children experiencing acute dyspnea may have problems with correct handling of the DPI.[95] It is recommended that alternative forms of aerosol delivery be considered during acute wheezing episodes, and that careful adult supervision ensure correct use by young patients.

Table 8. Advantages and Disadvantages of Dry Powder Inhalers for Aerosol Delivery

Advantages	Disadvantages
Efficient drug delivery	Limited range of available drugs
Portable	Possible airway irritation from dry powder
Short preparation and administration time	Possible reaction to lactose or glucose carrier
Little hand-breath coordination needed; no head tilt or breath-hold needed	Require high inspiratory flowrates
No chlorofluorocarbon propellant	Require loading before use
Easy count of drug doses	Less useful than other modes in acute obstruction

The need for high flowrates does not appear to be present with the terbutaline dry-powder multiple-dose inhaler, available in the United Kingdom as the Turbohaler and in Europe as the Turbuhaler. In a study of the device by Pedersen and co-authors,[96] the effect on the FEV_1 of children aged 7-15 years was virtually identical with inspiratory flowrates of either 60 L/min or 31 L/min. The investigators found that 42 of 57 children between 3.5 and 6 years of age could generate a peak inspiratory flowrate (PIFR) greater than 28 L/min. Therefore, a sizeable percentage of children as young as 3 years can use this device with good results. In the study, the Turbuhaler was reported to retain approximately 33% of its effect even at inspiratory flows of 13 L/min. Unfortunately, this device is not available in the United States at this

time (1991). Other improvements in the dry powder application include a breath-actuated inhaler, containing 400 doses of salbutamol (albuterol), triggered by inspiratory flows of 30 L/min, and a Diskhaler, an 8-dose reloadable device similar to the Rotahaler.[97]

DPIs have been shown to be as effective as MDIs.[98-100] Their simpler use makes this formulation an attractive alternative for aerosol delivery, with the qualifications noted. As newer multiple-dose devices that operate effectively at lower inspiratory flows become available in the United States, DPIs may become the prescription of choice for both adult and pediatric patients, replacing the MDI and bulky, cumbersome nebulizer systems.

Aerosol Delivery via Face Mask

With very young spontaneously breathing children or infants, aerosolized drugs are usually administered via a mask. The MDI-spacer-mask combination was previously noted, although a jet nebulizer with mask is more common. Little is known concerning the amount of drug that reaches the lung under these conditions of delivery. In a review article, Silverman[83] cites a number of factors that can affect mask delivery: particle size, the use and characteristics of a spacer, distance of the jet from the face, tidal volume, inspiratory flowrate and effect of nose-breathing. A study by Salmon and colleagues[101] has indirectly quantified the amount of cromolyn sodium reaching the lungs of infants with a mask. That study used urine-plasma ratio and the absorption kinetics of cromolyn to estimate lung delivery from amounts of the drug in the urine. Delivery from an MDI-spacer gave an estimated lung deposition of only 0.13% and from an Acorn nebulizer at 8 L/min only 0.33% of the total dose of 20 mg. An Intal-5 MDI with 4 puffs was used to equate the doses. In the same study, adults who were instructed to nose breathe, achieved a 0.65% lung deposition with the nebulizer. Although twice the infants' deposition rate, this is far below the usual 10-20% quoted for lung delivery of an inspired aerosol. In a study of clinical effect of face mask versus mouthpiece, Steventon and Wilson[54] found no difference in symptoms or peak expiratory flows. Flaws in that study have been previously noted. Until further data are available on mask delivery in infants, we must assume that a very small percentage of drug reaches the lung by this mode, and this is consistent with Salmon's indirect estimate.[101]

Aerosol Delivery in Intubated Patients

Despite the uncertainties surrounding aerosol delivery to spontaneously breathing patients, both adult and pediatric, the question of aerosol delivery to intubated and ventilated subjects seems to have become the topic of the day. This is evidenced in the excellent editorial by Hess in a recent issue of Respiratory Care,[102] and in the number of references to the oft-quoted 1985 study of MacIntyre and associates.[103]

Deposition Studies

Beginning with an abstract in 1981 by Fraser and co-workers,[104] data have accumulated on amounts of aerosol delivered through endotracheal tubes (ETTs) during mechanical ventilation. In general, the data show less deposition in the lung with this form of delivery compared to deposition in spontaneously breathing subjects. Table 9 summarizes the results of studies applicable to the adult and neonatal-pediatric population.[103-109] In those studies, lung deposition ranges from 1.22% to 5.65% for adults, and 0.19% to 0.69% for neonates and children. The percentage of total dose deposited with MDI and nebulizer in nonintubated subjects is usually given at 10%, and under optimal conditions with an extension chamber at as much as 20%.[110,111] For intubated infants, lung deposition of approximately 0.5% is only 1/20th that seen in the non-intubated adult and about 1/10th that of an intubated adult's average of 5%. This suggests the need for a much larger dose of drug to have an equivalent dose deposited in an intubated infant. Whether this is necessary for maximum clinical effect must be determined by appropriate dose-response studies to account for other variables such as age, lung development, and ventilatory variables.

The primary factor reducing lung deposition in intubated subjects is theorized to be the baffling

Table 9. Summary of Studies Examining Percentage of Aerosol Dose Reaching the Lung in Intubated Subjects

Tube Size	Device	% Deposition	Comments	Reference
Adult Studies				
> 7 mm	SVN*	2.9 ± 0.7	In vivo, proximal	MacIntyre et al[103]
8.0 mm	SVN	1.62 ± 1.28	Abstract only	Fraser et al[104]
Unspecified	SVN	1.22 ± 0.35		
	MDI	5.65 ± 1.09	Extension chamber	Fuller et al[105]
7.5 mm	MDI	4.7 ± 3.2	In vivo, proximal	Crogan et al[106]
Neonatal-Pediatric Studies				
3.0 mm	SVN	0.19 ± 0.1 to 1.96 ± 1.19	Rabbit model	Flavin et al[107]
Unspecified	SVN	0.28 ± 0.1	Newborn piglets	Banks et al[108]
3.5 mm	SVN†	0.69	In vivo, filters	Cameron et al[109]
	USN	0.60		

*SVN = small volume nebulizer; MDI = metered dose inhaler; USN = ultrasonic nebulizer.
†Average with 4 types of nebulizer: Ultravent, Acorn, MAD2, SPAG.

effect of the ETT on inertial impaction of particles. This was clearly evidenced in Crogan and Bishop's study,[106] which found that the smaller the ETT, the less aerosol was delivered through to the airway. Another study by Flavin and associates[107] showed that out of the small amount of drug reaching the airway, 60-90% stayed in the ETT and 10-40% reached the lung, further reducing the amount acting on the target organ. MacIntyre's results[103] contrast somewhat by showing that only 28% of the dose stays in the ETT, although that study had few subjects (7 intubated) and was vague on the exact method of aerosolization. Presumably an IPPB device was used, which can affect the results on deposition.[112] Extrapolating from these results can lead to the conclusion that very little aerosol gets through an infant-sized airway, which is consistent with the animal model and lung model studies in Table 9.

Results of the studies of Girard et al[113] and Ahrens et al[114] contradict the notion that deposition of aerosol in intubated subjects is generally less than in unintubated subjects. The first is an adult study that compared plasma concentrations of aerosolized pentamidine in intubated and non-intubated subjects.[113] Girard and associates found peak plasma concentrations of aerosolized pentamidine in adults of 65.6 ± 9.4 μgs/L in unintubated, but 215.8 ±49.8 μg/L in the intubated subjects. This implies a higher lung deposition with intubation and ventilation than with spontaneously breathing subjects, which contradicts the literature showing reduced ETT delivery of aerosols. The authors speculated that this may be due to: reduced loss with the inline ventilator system (which is unlikely), reduced particle size with high inspiratory flowrate, and possibly increased alveolocapillary uptake due to the inflammatory process of pneumocystis pneumonia. The nebulizer used was an ultrasonic (DeVilbiss UltraNeb 99), which produces a particle size of 4.6 μm MMAD (not especially small for peripheral deposition). Perhaps more significantly, the ultrasonic replaced the humidifier in the inspiratory limb of the ventilator circuit.

The in-vitro study performed by Ahrens and associates,[114] found reduced delivery of aerosol to the lung with a conventional jet nebulizer (Intec Fan Jet) producing a MMAD of 3.4 μm. However, the delivery to the lung was still higher than the studies referenced in Table 9, with over 25% delivery using a 3.0-mm ETT and an inspiratory flowrate of 7.5 L/min in their ventilated lung model. The surprising aspect of the study was that a submicronic aerosol generator (Mallinckrodt Ultravent) that produced a MMAD measured at 0.54 μm at the nebulizer outlet, delivered 78-99% of

the dose beyond the ETT, with 3.0-mm-, 6.0-mm-, and 9.0-mm-diameter tubes at various flowrates. This contrasts sharply with Flavin et al's in-vivo study on piglets that showed 0.70% to 1.96% deposition through a 3.0-mm ETT with the same Ultravent nebulizer.[107] Flavin et al measured particle size at 0.80 μm MMAD by the same method as used by Ahrens (a 7-stage cascade impactor). Fuller et al,[105] in discussing aerosol delivery results with intubated patients, comment that pilot laboratory models at their center showed considerably greater deposition than in-vivo studies. Silverman's review article[83] offers a possible explanation for the difference in in-vitro and in-vivo studies by pointing out that using filters to assess delivery may be inaccurate. Rainout of aerosol in the tubing may contaminate the filter by dripping, adding considerably to the dose estimate from weight of the filter. This occurrence was explicitly acknowledged in Ahren et al's study,[114] and may help explain the high delivery results obtained.

If the contradictory results cited are not in fact representative, the conclusion that aerosol delivery to the lung decreases with smaller-sized ETTs has implications for intrapulmonary delivery and distribution of aerosols in infants. At birth, an infant has tracheal dimensions of 4-6 mm diameter with 40-mm length, compared to an 18-mm diameter and 120-mm length in the adult.[115] Bronchi and bronchioles are similarly smaller. In addition to particle baffling by small ETTs, a reduction in airway size has been shown to cause reduced penetration of aerosols.[116] If small aerosol particles of 2.0 μm are needed to reach peripheral airways in adults (approximately 2 mm in size), even smaller particles may be needed to penetrate beyond the trachea of intubated infants. Otherwise no effect on the infant's peripheral airways will be seen. At this time, optimal aerosol size distributions for infants are not known.

Variables in Delivery Methods

The confusing array of possible configurations for aerosol delivery systems to intubated subjects makes interpretation or reconciliation of conflicting results difficult (as with the larger question of aerosol delivery, in general). At least eight variables have been studied in the research literature.

1. The position in the ventilator circuit of either the nebulizer or the MDI device is one variable that has been examined.[117] Results suggest that positioning an aerosol generator upstream from the Y-piece connected to the ETT increases the amount of aerosol reaching the tube and ultimately the lung. This is consistent with Fuller's study,[105] in which a MDI coupled with a 5 × 10-cm extension chamber placed 20 cm before the Y-piece improved deposition. In that study, the MDI outperformed nearly five-fold a nebulizer placed 70 cm upstream from the Y-piece. The practice of placing either type of aerosol generator at the patient Y or directly on the ETT is not supported by these results. Yet, a recent survey by Salyer and Chatburn[118] found that in 54% of neonatal and 59% of pediatric patients aerosols were administered by nebulizer inline at the patient Y.

2. Use of a mechanical ventilator introduces a number of additional variables that can affect aerosol delivery including flowrate, peak pressure, and tidal volume; respiratory frequency; inspiratory, expiratory versus continuous nebulization; inspiratory time or I-E ratio; and mode of ventilation. Results of a number of investigations have been presented only in abstract form.[119-121] This fact plus the number of variables introduced with ventilatory assistance have created a need for comprehensive systematic investigation in fully described studies. Results from two centers are compared in Table 10.[119-122] It is interesting that no agreement exists on variables such as tidal volume and frequency, examined in both centers. A partial explanation may be the substantial differences between protocols. The Swedish study of Dahlbäck and associates[122] utilized a system in which a jet nebulizer (Viasol, MA2) is operated during the expiratory phase only and the duration of nebulization is controlled. For example, nebulization could be set to occur only during the last half of the expiratory phase. The Loma Linda nebulizers (AeroMist, AeroTech II, Ultravent) were run continuously, inline with the ventilator circuit.[119-121]

Table 10. Relationship between Ventilatory Variables and Aerosol Delivery in Studies Conducted at Loma Linda University Medical Center and the University of Lund, Sweden

Variable	Effect on Aerosol Delivery	
	Loma Linda[119-121]	Lund[122]
Nebulizer flowrate	Aerosol increased as flowrate increased	Not examined
Nebulizer-to-Y volume	Uncorrelated	Aerosol increased as volume increased
Peak pressure increase (ie, increased V_T)	Aerosol increased as pressure increased	Uncorrelated
Respiratory frequency	Aerosol increased as frequency increased	Aerosol decreased as frequency increased
Duration of nebulization	Not examined	Aerosol increased as nebulization time increased

3. Specific areas of the lung may be targeted for aerosol delivery by manipulating breathing pattern and particle size. This supports the view that ventilatory variables influence drug delivery and need to be studied. Dahlbäck and associates[123] found that peripheral versus central lung deposition was 60% and 40% with deep slow breaths of 0.5-μm particles, and shifted to a 30% and 70% pattern with rapid shallow breaths of 2 μm particles. The study was performed on tracheotomized rabbits, making it applicable to infants, although airway size was not specified.

In order to investigate the clinical utility of tailored particle sizes, one needs to correlate the specific drug agent with the site of the target receptors in the airway. As a specific example, beta$_2$-receptors are found throughout large and small airways.[124-126] Because the peripheral airways comprise the largest cross-section of conductance, it is reasonable to hypothesize that beta-agonists should be targeted to the periphery for greater bronchodilating effect. This has, in fact, been substantiated by two separate studies.[127,128] For example, Patel and associates[127] found greater effect on forced expiratory flow at 25% and 75% of vital capacity ($FEF_{25-75\%}$) with 2.5 μm particles of isoproterenol compared to 5.0 μm. Yet, two different studies have presented other results that seem to contradict this effect of particle size.[129,130] Both studies examined the influence of nebulizer flowrate, which determines the particle sizes a nebulizer produces, on expiratory flow after bronchodilator administration.[131] The studies used FEV_1 and PEFR, which are measures of large airway function. Neither of these studies could detect an effect on small airways, providing yet another example of study methodology causing differences among reported results.

4. The question of manual versus ventilator delivery of aerosol was examined in an abstract by Henry and Chatburn.[132] Under the conditions of their study, manual ventilation with continuous nebulization by a Puritan-Bennett Raindrop nebulizer was less effective (2.46% ± 3% delivered) than intermittent nebulization with a Bennett MA-1 (25.8% ± 3%). The nebulizer was placed at the manifold upstream from the Y.

5. It should be realized that addition of a continuously operated nebulizer inline with a ventilator circuit can affect both volumes and pressures delivered to the patient. In an abstract, Salyer and associates[133] reported significant increases in peak pressures and tidal volumes during volume ventilation of an infant lung model when continous nebulization was used. Results at our own laboratory have been similar to Salyer's. Figure 3

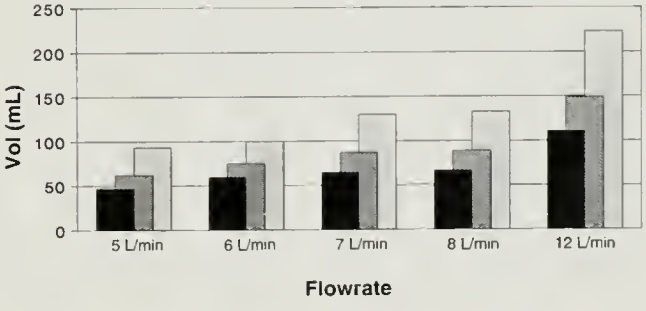

Fig. 3. Predicted volumes added to a ventilator circuit by an inline nebulizer, calculated from nebulizer flowrate and inspiratory time. Values are at body temperature and pressure, saturated (BTPS). ■ 0.5-s inspiration, ▩ 0.67-s inspiration, □ 1.0-s inspiration.

illustrates calculated volumes added by an inline nebulizer for varying nebulizer flowrates and inspiratory times. In an infant, these amounts can become large even with a ½-s inspiratory time. Based on the findings of Ahrens et al[114] and Dahlbäck et al[123] that smaller particles may improve deposition with small ETTs, higher rather than lower nebulizer flowrates would be needed. This is based on the fact that the size of particles produced by a jet nebulizer decreases as nebulizer flowrate increases.[131] One text on respiratory care for neonates and children[46] states that nebulizer flowrate should be adapted to the patient's respiratory pattern and that a flow of 4 L/min is sufficient for a resting infant. This recommendation ignores the fact that flowrates greater than 8 L/min are needed with some nebulizers to produce particle sizes smaller than 5 μm.[131] This holds for both spontaneously breathing and intubated subjects. Because higher flowrates also waste a good deal of the dose during expiration, newer systems of delivery, including ones with lower flowrates, are needed for infants and children. Continuous inline nebulization can inactivate alarms, adversely affect expiratory flowsensors, and complicate pressure-supported ventilation.[134]

Even an MDI can add appreciable volume when discharged into a ventilator circuit. Measurements at this institution (unpublished) have shown mean volumes of 53 mL per discharge for Proventil MDIs and 72.5 mL per discharge for Atrovent MDIs. We also noticed that MDI volume delivery (and, therefore, possibly drug delivery) was reduced with discharge against an opposing pressure.

6. Results of studies on aerosol delivery of drugs are not consistent with respect to the particle size produced by various generators. Table 11 reports particle sizes given for the Mallinckrodt Ultravent (formerly the SynteVent) in four different studies.[107,109,114,135] Sizes range from 0.31 μm to 1.8 μm, an almost 6-fold difference. At least two factors can influence the measurement of particle size: the site where the particle is sampled and the method of measurement. Because this affects interpretation of results, I recommend that site and method of measurement be reported in all studies of aerosol delivery in which such measurements are made and that therapeutic delivery conditions be reproduced to the extent possible.

7. Another source of variability in aerosol drug delivery is the lack of equivalent doses with MDI and nebulizer administration. For example, the recommended MDI dose of albuterol in the United States is 0.180 mg (90 μg/puff, but the nebulizer dose is 2.5 mg.[53] This is a 14-fold difference in strength. Yet, the entire literature states that approximately 10% of the dose, by either nebulizer, MDI, or MDI with an extension, reaches the lung.[79,110,111] The difference is simply where the remaining 90% or so is lost: room and nebulizer apparatus, oropharynx (MDI), or holding chamber (MDI with extension).[136] If the lung deposition fraction is truly the same, then very different doses are being given with these different methods of administration. Several studies using identical doses have shown that 2- to 4-fold response differences are seen with nebulizer versus MDI.[136-138] This

Table 11. Comparison of Aerosol Particle Sizes Produced by the Ultravent Nebulizer and Measured at Various Sites by Various Methods

Investigators	Particle Size (microns)	Site	Method
Flavin et al[107]	1.8	Nebulizer	Laser
	1.2	End of ETT*	Laser
Cameron et al[109]	0.8	Unspecified	7-stage cascade impactor
Ahrens et al[114]	0.54	Nebulizer	7-stage impactor
	0.49	Main-stem bronchus, 3-mm ETT	
	0.54	Main-stem bronchus, 6-mm ETT	
	0.49	Main-stem bronchus, 9-mm ETT	
Dahlbäck et al[135]	0.31	Unspecified	Electrical aerosol analyzer

*ETT = endotracheal tube.

suggests that different lung deposition rates exist for MDIs and nebulizers, but that the difference is not 14-fold as the dose difference implies. Recent adult studies have recommended MDI doses 2½ × higher than customarily prescribed to achieve results equivalent to results via nebulizer delivery.[139,140] This is consistent with the 2- to 4-fold difference reported. The use of equipotent doses (that is, doses that give the same amount of bronchodilation) requires dose-response studies not just for the drug but for the drug with the specific method of delivery. The preliminary studies cited have begun to dispel the myth that an MDI is less effective than a nebulizer. Patients simply may have been underdosed with the MDI. To summarize, comparisons of aerosol delivery methods require equipotent doses among the methods to avoid confounding the results. This probably will require 1:2 or 1:4 of doses between MDI and nebulizer rather than the 1:14 ratio currently seen in commercial aerosol drug preparations. This is achieved by increasing the number of puffs from the MDI—not by reducing the nebulizer amount.[10]

8. A possible inaccuracy when nebulizer drug output is estimated from weight loss from the nebulizer solution has been pointed out by O'Callaghan.[141] For example, if 2 mL of cromolyn sodium 20 mg is nebulized, and the weight equivalent of 1 mL of solution is lost, then the delivered dose is customarily calculated as 10 mg. O'Callaghan and associates compared calculated values to assays of the aerosol cloud produced and concluded that weight calculations overestimate drug output because some of the liquid evaporates and is not delivered.

Summary and Conclusions

My analysis of the literature suggests that:

- Equipment specifically designed for efficient nebulizer delivery of aerosols to infants and children is needed;
- the numerous variables in the delivery system can cause variation in research results for aerosol delivery to infants and children;
- the investigational protocol (specifically, the variable measured to determine outcome) can further cause differences in conclusions affecting results.

Further, analysis of the literature leads me to conclude and recommend:

- Aerosol delivery through an ETT is less than delivery through the unintubated airway.
- Smaller aerosol particle sizes may be needed to increase dose delivery, with both ETT and small infant airways.
- Alternatively, larger doses of drug may need to be aerosolized to compensate for reduced delivery.
- Equipotent doses for nebulizer and MDI delivery range between 2:1 and 4:1 but formulated strengths range from about 10:1 to 14:1.
- Dose-response studies are needed with equipotent doses when different delivery modes are used or compared. This is likely to require higher MDI dosages than previously used.
- Clinical effect should be correlated with quantitative deposition studies.
- Studies on aerosolized drug delivery should include full specification of all details of the delivery system.
- The lack of consistency in the effect of ventilatory variables on aerosol delivery and clinical effect, reported in numerous abstracts, needs to be resolved by the results of well-executed studies reported in peer-reviewed journals.

CLINICAL EFFECTS OF AEROSOLIZED DRUGS IN NEONATAL AND PEDIATRIC PATIENTS

Most aerosolized drug therapy is targeted at infants who wheeze and pediatric subjects with reactive airway disease. Drugs given by aerosol to this population include beta-adrenergics, anticholinergics (ipratropium bromide), cromolyn sodium, corticosteroids, and ribavirin.

Controversy exists in the literature regarding the efficacy of aerosolized beta-agonists in young infants, and is acknowledged in the introduction of many research studies on the subject. There is less questioning of the efficacy of aerosolized drugs, both bronchodilators and others, in children. Consequently, in discussing the use of aerosols in infants, I emphasize the bronchodilators and provide only a summary of other drug classes.

Beta-Adrenergic Bronchodilators

The question of the effectiveness of beta-adrenergic bronchodilators in infants raises two

issues: the nature and cause of the airway obstruction and the presence of smooth muscle and beta-receptors in neonatal and infant airways. The question is further complicated by the two variables already discussed and well-stated in Kelly's excellent review:[15] the lack of adequate objective measures of obstruction in infants and the difficulty in delivering aerosols to infants.

Table 12. Causes of Wheezing in Infants and Children

Asthma
Aspiration
Bronchiolitis
Cystic fibrosis
Foreign body
Bronchopulmonary dysplasia
Left ventricular failure
Mediastinal masses
Tracheomalacia, bronchomalacia
Tracheal webs or tracheal stenosis
Vascular rings

The Pathophysiology of Wheezing

Wheezing is the clinical sign that usually leads to bronchodilator trial. Wheezing can be produced by the causes listed in Table 12. To paraphrase the old asthma axiom, not all that wheezes responds to bronchodilator therapy. For example, wheezing caused by mediastinal masses, fluid overload, or left-ventricular failure does not respond to bronchodilator therapy, but can usually be readily differentiated by history, clinical picture, and diagnostic testing. Bronchodilator therapy is most often utilized when wheezing is present in bronchiolitis, bronchopulmonary dysplasia (BPD), and cystic fibrosis. Acute bronchiolitis occurs with young infants and is almost always viral in origin.[41,142] About 50% of infants with acute bronchiolitis exhibit wheezing, and approximately the same proportion subsequently develop asthma.[41,143] Viral bronchiolitis, asthma, and BPD all involve inflammation of the airway.[144,145] The pathophysiology of bronchiolitis is well-described by Tabachnik and Levison:[41] Increased airway resistance and gas trapping with increased residual volume and functional residual capacity (FRC). This increases the elastic work of breathing. The problem for bronchodilator therapy in these disorders is that the cause(s) of obstruction can vary. Inflammation of the airway results not only in smooth muscle constriction but also in mucosal edema, excess mucus secretion, epithelial sloughing, and intra-luminal cellular debris, as illustrated in Figure 4.[41,144,146,147] The relative contribution of these multiple processes of inflammation affects bronchodilator response.[148] Smooth-muscle constriction responds most readily to bronchodilators with a fall in airway resistance. Relaxation of smooth muscle may cause varying effects on wheezing when the other causes of obstruction (edema and secretions) are present, including an increase in wheeze as air

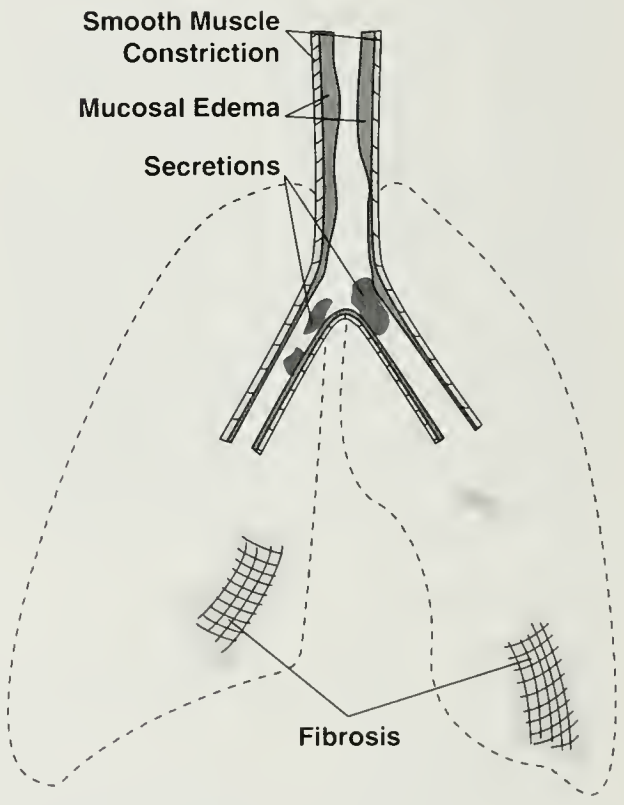

Fig. 4. Components that can contribute to airway obstruction with inflammatory disorders such as viral bronchiolitis or bronchopulmonary dysplasia (BPD). Such obstruction leads to gas trapping (with increases in residual volume and decreases in vital capacity) and increases in airways resistance, with a consequent increase in work of breathing.

moves past the obstruction. Bronchodilators do not directly reduce edema, fibrosis, or secretions. As a result, even when such drugs are restricted to the disorders of wheezy bronchiolitis and asthma, it is not possible to predict response without an empirical trial of therapy. Better techniques for assessing the role of mucus, edema, and smooth muscle in airway obstruction could improve criteria for use of bronchodilator therapy in these disorders.

Presence of Beta-Receptors in Neonates

Research over the last 10 years illuminates the question of beta-receptors in neonatal airways.[124,149,150] Using the technique of radioligand binding, the following conclusions have been reached:

- Beta-adrenergic receptors are present and functional in the human fetal lung as early as the second trimester.[149]
- Beta-adrenergic receptor concentration increases with gestational age.[149]
- $Beta_2$-receptors predominate in human fetal lung.[149]
- Receptor affinities for agonists seem to be greater in young animals compared to older ones.[124]
- Receptor densities are lower in tissues of young animals.[124]
- Wheezing infants in the first year of life have highly effective $beta_2$-receptors as evidenced by the ability of salbutamol to abolish the reponse to histamine challenge.[150]

These findings are consistent with those of Roan and Galant,[151] who found a decreased number of beta-receptor sites in neonatal cord-blood neutrophils compared to the number of sites in adults. Most species exhibit ontogenetic changes in receptor response and density.[152,153] Insel and Motulsky[153] caution against use of blood cells to study adrenergic receptors because such cells may not reflect the properties or response of other tissues such as bronchial smooth muscle.

It is also generally accepted that exposure of beta-receptors to beta-agonists or catecholamines causes a down-regulation of response—in effect, a desensitization.[152] This response can be reversed with some hormones such as glucocorticoids, which seem to increase beta-receptor expression or density on cell surfaces.[153,154] It is possible that catecholamine secretion during the stress of delivery can down-regulate beta-receptors and temporarily decrease the response of neonatal airways to beta-agonists.[151]

Studies of Beta-Adrenergic Bronchodilators in Infants and Children

The use of aerosolized beta-adrenergic bronchodilators in infants has been questioned on the basis of early negative studies.[155-160] Most often quoted is the study by Lenney and Milner[158] showing that response to bronchodilators is not seen until after 20 months of age. It has been thought that lack of response is due either to lack of beta-receptors in the airway or to insufficient development of bronchial smooth muscle in neonates and young infants. The 1972 study by Matsuba and Thurlbeck[161] is often referenced to support underdeveloped smooth muscle, although that study simply demonstrated a lower ratio of smooth muscle to bronchial wall in pediatric small airways. Increasing indirect evidence for the presence of bronchial smooth muscle comes from studies showing a positive response to aerosolized bronchodilators in neonates and infants. Table 13 lists studies with both positive and negative results for aerosolized beta-adrenergic bronchodilators. This listing includes neither studies on children nor studies combining a beta-adrenergic and an anticholinergic drug. Those studies are summarized separately.

Table 13. Summary of Studies on Aerosolized Beta-Adrenergic Agents in Infants

Positive Response	No Response
Kao et al,[163] 1984	Phelan & Williams,[155] 1969
Sosulski et al,[164] 1986	Radford,[157] 1975
Gomez-Del Rio,[47] 1986	Rutter et al,[156] 1975
Motoyama et al,[48] 1987	Lenney & Milner,[158] 1978
Mallol et al,[166] 1987	Lenney & Milner,[159] 1978
Cabal et al,[165] 1987	Stokes et al,[160] 1983
Prendiville et al,[175] 1987	Sly et al,[162] 1991
Rotschild et al,[168] 1989	
Brudno et al,[167] 1989	
Mallory et al,[49] 1989	
Schuh et al,[50] 1990	

It is interesting that the 7 negative studies were performed in England (with the exception of 1 in Australia)—and 4 were performed at the same center, with at least 1 of the same investigators involved in 4 of the studies. A definite chronologic difference exists between negative and positive studies. With one exception,[162] studies since 1984 have been positive, and the number has increased steadily. The three factors causing variability in response to bronchodilator could have caused the previous negative results: lack of a sufficiently sensitive technology of measurement, inadequate delivery/dose of the agent, or the presence of airway obstruction due to causes other than bronchospasm. None of the infants in the negative studies was intubated. Most used a face mask both for delivery of the nebulized drug and for measurement by the forced oscillation method. In one study utilizing whole body plethysmography, investigators attached the nebulizer to a nasal adaptor fitted into the infant's nose.[157] With the highly efficient filtration of particles in the nose, it is possible that an insufficient amount of drug was delivered to the lower airways.

The increasing number of positive studies with beta-adrenergic bronchodilators is itself evidence for adequate bronchial-smooth-muscle and beta-receptor development in infants.[47-50,150,163-169] In fact, the more recent studies (since 1984) have used younger infants (mean age 3.20 mo, range 3 d to 24 mo) compared to the earlier studies (mean age 6.3 mo, range 1-43 mo). Sample size on the average remains similar (recent 22.3 versus earlier 19.4), but several of the newer studies have been quite large with 30, 40, and in one case 79 subjects.[47,48,166] These numbers represent a crude meta-analysis performed over all of the studies in Table 13. The explanation of less smooth-muscle and beta-receptor development used in the older negative studies is increasingly and strongly contradicted by the more recent studies in younger infants.

Two studies, in particular, support the use of beta-adrenergic bronchodilators in neonates and infants and contradict the conclusions of older studies.[170,171] The first is an investigation by Tepper[170] in which he studied 10 normal infants below 15 months of age without signs of wheezing. The youngest was 3.5 months, and the mean age was 8.1 months. The rationale for utilizing normal subjects was to demonstrate the reactivity of bronchial smooth muscle by eliminating the confusing variables of edema and mucoid or cellular obstruction of the airway thought to be present in infants with viral bronchiolitis or BPD. Tepper's study showed that the infants developed bronchoconstriction following methacholine challenge that could be reversed with inhaled metaproterenol 0.025 mL/kg delivered by Inspiron nebulizer at 10 L/min. The author did not state whether a face mask was used or whether infants were intubated. Maximal expiratory flow at FRC ($\dot{V}_{maxFRC}$) was measured to assess lung function using the partial expiratory flow-volume method. The reversibility of the methacholine-induced fall in $\dot{V}_{maxFRC}$ by the beta-adrenergic drug demonstrates the presence of reactive, functional smooth muscle in infants. It also demonstrates that an aerosol reaches the lung in sufficient amounts to produce an effect.

A second study by Kraemer and colleagues[171] showed that systemically administered albuterol 0.225 mg/kg reduced lung hyperinflation and airway resistance in 74% of 60 infants with respiratory distress syndrome, wheezy bronchitis, or cystic fibrosis. The systemic route of administration eliminates the variability due to differences in aerosol delivery systems. However, the presence of differing pathophysiologies remains a confounding factor—one that was not present in Tepper's study.[170] Because not all subjects responded, the results support the conclusion that airway obstruction is not solely due to bronchospasm and, therefore, not always responsive to bronchodilator. Beta-adrenergic agonists have been investigated in children including adolescents.[35,51,172,173] There is less controversy with this age group, and optimal doses for one particular beta-agonist (metaproterenol) has been established for 3-to-6-year olds.[35] This dose was determined to be 0.01 mL/kg, up to a maximum of 0.3 mL of a 5% solution.

An interesting feature seen in both infants and children is the variability of response to beta-agonists, previously mentioned. Schuh and co-workers[172] examined and compared two doses of albuterol in acute childhood asthma. Their findings may be relevant to the use of these drugs in young subjects. The lower dose investigated was the standard dose of 0.15 mg/kg body weight (0.03 mL/

kg, 0.5% solution). At this dose, greater individual variability in response (including no response) was seen than at a higher dose of 0.30 mg/kg body weight (0.06 mL/kg). This finding raises the possibility that in addition to the factors of the aerosol delivery system and pathophysiology, doses of beta-agonists may be inadequate. The variable degree of response, including absent or negative responses, has been seen in those positive studies that report individual results.[47-49,150,168] Similar results had been reported in a previous study by Schuh and associates,[51] comparing 0.05 mg/kg to 0.15 mg/kg nebulized albuterol in children 5 to 17 years of age with acute asthma. Again, the higher dose was more effective. Paradoxical responses to bronchodilators have been reported in the literature in adults, children, and infants.[174-177] The Food and Drug Administration (FDA) received 126 reports of paradoxical responses associated with MDI use between 1974 and 1988, and 58 reports associated with nebulized solutions between 1983 and 1988.[174] This represents a small fraction considering the numbers of patients using both types of device. These responses usually consist of bronchoconstriction or respiratory irritation but have also included headache, tremor, psychosis, and cardiovascular reactions. Speculated causes of bronchospasm associated with MDI use include turbulent airflow with incorrect inhalation and reaction to the propellant or to additives and preservatives (eg, alcohol and/or oleic acid).[178] Nebulized solutions may cause bronchospasm by means of their tonicity, acidity, or additives such as benzalkonium chloride.[175-177,179]

Anticholinergic Bronchodilators

A study in 1983 reported no response to nebulized ipratropium, 250 μg every hour, in acute bronchiolitis, with 66 infants (mean age 130 d).[180] It is surprising that the same three investigators in that study had reported two previous studies showing improvement with nebulized ipratropium (250 μg) in viral bronchiolitis.[160,181] The difference in results may well be due to the outcome variables measured. The negative study assessed only clinical signs (cough, nasal flaring, cyanosis) rather than measures of pulmonary function as in the two positive studies.[160,181]

Several other studies[52,182-186] have documented a positive response to anticholinergic bronchodilators in infants and children. Two aspects of these positive studies should be noted. First, although these studies were able to show group improvement in infants and children younger than 3 years, individual subjects did not always show improvement. This was also seen with the beta-agonists. In Hodges' study,[182] approximately 40% of the pediatric subjects under 18 months of age showed a positive response in lung function. The variable response may be dose-related (representing inadequate aerosol dose delivery to these young patients) or may indicate a nonresponsive obstructive pathology. Second, it is unclear whether combining an anticholinergic with a beta-agonist produces an additive effect. Several studies have shown greater improvement in lung function with combined therapy.[181,184-192] However, at least two investigations concluded that no increase in effect occurs with combinations.[183,193] The patients in one of these two studies were infants with BPD rather than asthma as in the other studies.[183] Some variability in response was seen in the positive study by Lew and associates[190] in which combination therapy was superior in only 11 of the 17 children (65%) studied. Similarly, a positive study by Storr and Lenney[185] showed a greater response to combined treatment during mild asthma but not during severe acute asthma.

In summary, it appears that anticholinergic bronchodilators such as ipratropium are beneficial in airway obstruction with a bronchospastic component, but other variables such as dose, delivery efficiency, disease state, and, perhaps, individual variation can influence their effectiveness.

Other Aerosol Drug Classes

Cromolyn sodium, corticosteroids, and ribavirin are frequently delivered via aerosol to infants and children. The clinical efficacy of each is summarized from the literature.

Cromolyn Sodium

Cromolyn sodium (Intal), also termed sodium cromoglycate or disodium cromoglycate, is considered to be a prophylactic antiasthmatic drug

and is often described as a mast-cell stabilizer. At least one study purports to show that the site of action of the drug is predominantly small airways reached with particles with a 2.0 μm MMAD.[194] The drug is currently available in three formulations in the United States: Spinhaler (powder), solution for nebulization, and metered dose inhaler.[53] These formulations contain dose differences. Both the powder and solution provide 20-mg doses, whereas the MDI is 0.8 mg/puff (usual dose = 1.6 mg, or 2 puffs).

At least one study[195] reported no difference between cromolyn sodium and placebo in improvement in wheezing, cough, sleep disturbance, and use of other drugs in children aged 1 to 4 years with wheezy bronchitis. However, a number of other studies have reported positive results, consisting of reduction of symptoms, protective effect equal to theophylline, improved pulmonary function, and parental preference for cromolyn therapy.[196-201] These studies included infants, preschool children, school-age children, and adolescents. Not all subjects are protected by prophylaxis with the drug. In a study by Corkey and associates,[202] cromolyn was considered to be clinically effective against exercise-induced bronchospasm in 59% of the studies on 18 asthmatic children and adolescents.

Two types of variability have also been noted with use of this drug in infants and children. First, the protective effect is not seen in children below 1 year of age.[198,200] This may well be due to technical delivery problems causing ineffective dosages when age is considered. The study by Salmon and associates,[101] previously cited in the section on aerosol delivery systems, specifically investigated administration of cromolyn solution by mask in toddlers and showed that extremely small amounts reached the lung. Despite these results, O'Callaghan and associates[201] showed a protective effect with nebulized cromolyn delivered by mask in 13 infants (mean age 9.8 mo, range 3-19 mo) when challenged with nebulized water.

The second variability in clinical effect is seen with different formulations of the drug. The MDI form, with its lower dose (approximately 2 mg vs 20 mg for nebulizer solution and powder) has been shown to be less effective than either the powder or nebulizer solution.[203-205] This may be similar to the apparent lack of effect with beta-agonists given by MDI compared to nebulizer solution, discussed in Section 3 (Aerosol Delivery Systems). As with the beta-agonists, the ratio of MDI medication to nebulizer medication is approximately 1 to 10, and this may give ineffective amounts by MDI. No difference has been shown between the powder formulation with and without the lactose carrier agent.[202]

Inhaled Corticosteroids

None of the four currently approved aerosol glucocorticoids in the United States gives dosage guidelines for children under 6 years of age (Section 2). However, these agents have been investigated for pediatric application and are used in preschool children. There is general agreement that inhaled corticosteroids can be effective and safe in children, in reducing or replacing oral steroids and controlling asthma.[206-211] Use of a spacer device has allowed children as young as 12 months to benefit from MDI delivery of these drugs.[207,211] An extension device is recommended whenever corticosteroids are delivered by MDI to reduce oropharyngeal deposition and the consequent likelihood of oral candidiasis.[91] Recently, nebulized beclomethasone dipropionate was reported to produce improvement in lung function in infants aged 15-36 weeks with persistent wheezing.[212] A dose of 100 μg three times daily was administered for 2 weeks by jet nebulizer (no brand specified).

Use of intramuscular dexamethasone in conjunction with combined oral and inhaled salbutamol gave twice the rate of improvement in wheezing infants aged 1 to 12 months.[213] Although the dexamethasone was not inhaled, this beneficial effect demonstrates both the potentiating effect of corticosteroids on beta-adrenergic response and a possible anti-inflammatory effect of reducing airway obstruction due to causes other than bronchospasm (eg, edema, cellular debris, and respiratory secretion production).

Ribavirin

Respiratory syncytial virus (RSV) has been shown to be the principal pathogen in the majority of cases of acute infantile viral bronchiolitis.[143] The aerosolized antiviral ribavirin (Virazole) is specif-

ically indicated for treatment of this infection and is the only aerosolized drug with dosage guidelines developed for infants. The drug has been shown to reduce viral shedding and clinical signs of severity.[214-216] Administration of ribavirin is indicated in the treatment of severe RSV infections in infants with underlying cardiopulmonary disease or otherwise at risk.[217] Questions have arisen concerning the cost-benefit ratio of ribavirin in relation to outcome measures such as duration of hospitalization. A recent study[218] reported in abstract form has shown that ribavirin administered to mechanically ventilated infants with RSV significantly reduced the duration of ventilation, administration of supplemental oxygen, and hospital stay. A great deal of concern has been expressed over side effects to health-care personnel and patients. Until further data are available, pregnant or potentially pregnant caregivers should avoid exposure to the aerosol in light of its possible teratogenic and mutagenic effects. A recent editorial in this journal called for stringent environmental isolation for areas of delivery, including barrier protection (mask, gloves, gown, eyewear) for personnel.[219] A containment system for administering ribavirin to infants has also been reported.[220] Following the principle that drugs are the lesser evil compared to illness, no needless exposure to a drug should occur. Development of readily available and economical containment systems for the delivery of this and other aerosol drugs should continue. Administration of ribavirin with intubated and ventilator-supported infants creates additional potential problems addressed by Demers and coworkers.[221] In general, antiviral drug therapy is difficult and complex. I believe that additional development and investigation in this area of therapy is certain to be forthcoming.

Summary and Conclusions

The clinical efficacy of aerosolized drugs of various classes in neonatal and pediatric patients can be summarized:

- Beta-agonists have been shown to be effective in neonates and infants.
- Individual variation in response to bronchodilators exists and may be caused by delivery variables, nature of the airway obstruction in wheezing infants, or the technique of measurement.
- Beta-adrenergic and anticholinergic bronchodilators are most likely additive in their effect, especially in asthmatic children.
- Dose-response studies should establish effective doses and equipotent doses for MDI, MDI with spacer, and nebulizer delivery of drugs.
- More sensitive criteria to differentiate bronchoconstriction from other components of obstruction in wheezing bronchiolitis may help predict bronchodilator responders.

CONCLUSIONS

It is difficult to form a single conclusion given the diversity and variability in the literature on aerosolized drug delivery in this population. Detailed summaries and recommendations have been given at the end of Sections 3 and 4. Several of these form a common theme in both sections.

- the need for detailed specification of the aerosol delivery system in any study of aerosol drug therapy
- the need for dose-response studies, including the identification of equipotent dosages when differing delivery vehicles are used (MDI versus nebulizer)
- the need for improved efficiency in nebulizer delivery to infants and children, with smaller particle sizes at lower flows

Aerosolized drug delivery in neonatal and pediatric patients is complicated by the number of variables in that delivery, by the outcome variable measured, and by variability in the pathology treated. Despite this, an accumulating body of evidence suggests that inhaled drugs are effective in this population. There is unquestionably a need for a revolution in infant aerosol delivery technology, to design improved systems for this population.

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Rau Discussion

Rodriguez: In the package insert, the use of ribavirin with mechanical ventilation is contraindicated; yet, it's advocated by some company representatives. This obvious inconsistency causes some dilemmas. Joe, can you shed any light on this situation from your findings?

Rau: The question of ribavirin, as you know, is completely up in the air, and I didn't really get into that other than to mention the drug. I would be more interested in your discussion rather than my comments to be quite honest with you. The bottom line (as nearly as I can tell from reading the literature) is that there are simply insufficient data. A lot of the concerns with ribavirin (both for ventilated and nonventilated patients) center on side effects—it's not just the ventilator. But the data are simply insufficient. There were only studies on rodents and not primates.

Secondly, the best approach right now is to be very cautious, which is what Kacmarek said in his recent editorial.[1] Specifically, I think it's sort of foolish to restrict the use of ribavirin and not use it with mechanical ventilation. Environmental contamination is easier to control during mechanical ventilation, as you know; but ribavirin administration does complicate mechanical ventilation and requires some time-consuming filter changes. As I understand it, the manufacturer is basically covering itself legally with that caution. The 1986 article by Demers et al[2] is the best I've seen discussing the administration of ribavirin. But it's a little bit foolish not to use it with mechanical ventilation because those may be the sickest children you encounter—the ones that need it the most.[3] There are questions, though, about the efficacy of the drug in terms of days of hospitalization and outcome. There's no question that it does decrease viral shedding. But, is it cost-effective? That is beginning to be the question.

1. Kacmarek RM. Ribavirin and pentamidine aerosols: Caregiver beware! (editorial). Respir Care 1990;35: 1034-1035.
2. Demers RR, Parker J, Frankel LR, Smith DW. Administration of ribavirin to neonatal and pediatric patients during mechanical ventilation. Respir Care 1986;31:1188-1195.
3. Smith DW, Frankel LR, Mathers LH, Tang ATS, Ariagno RL, Prober CG. Aerosolised ribavirin in infants requiring mechanical ventilation for severe lower respiratory tract infec-

tion caused by respiratory syncytial virus. Clin Res 1991;39(1):59A.

O'Rourke: Just a comment on ribavirin—an article by Outwater et al[1] from Boston describes how often and exactly how to change the expiratory limb of the ventilator to be able to use ribavirin safely during mechanical ventilation. As you pointed out, the environmental exposure can be minimized during mechanical ventilation.

1. Outwater KM, Meissner HC, Peterson MG. Ribavirin administration to infants receiving mechanical ventilation. AJDC 1988;142:512-515.

Koff: I would just like to ask about the experience of this group in using pulmonary function studies to individualize bronchodilator therapy. We at this point don't own a PFT system in our hospital, but we have been testing them for a number of years and really have found pulmonary function measurement very helpful in finding the correct dose and the best bronchodilator for a particular patient. I really believe that's a technique that we are going to see used more and more—one that will become our guiding light. Such measurements provide information to us, and will get us out of this dark area.

Rau: Any responses to that?

Orenstein: In the field of cystic fibrosis, a number of studies have looked at acute responses to bronchodilator agents delivered by inhalation. All kinds of responses have been found—some patients with positive response, some patients with negative response, and lots of patients with no response. But, very interestingly, Ed Pattishall[1] recently reviewed the literature in *Pediatric Pulmonology* and also looked at our own patients over a number of years in Pittsburgh, and showed somewhat disturbingly that a patient's response in January 1987 did not predict reliably that same patient's response in March, April, or May of 1987 or in 1988 or 1989. It may be that asthmatics are different or other patient populations may be different, but at least among patients with CF it looks like it is going to be very tough and probably not worthwhile to try to establish a perfect dose for a given drug because a few months later or even a few days later the response may be very different.

A further point about what happens over a longer time than the few minutes that you have in the lab or by the bedside—there may be some positive or negative responses to these inhalational agents that we use that don't show up immediately after treatment. You may see that things that have been reported to occur with inhalation of beta agonists—for example, having to do with the effects on ventilatory muscle endurance[2] and effects on mucociliary transport rates,[3] things that you wouldn't be picking up with a quick FEV_1 or even full spirometry immediately after the inhalation—make it tougher to evaluate all these agents.

1. Pattishall EN. Longitudinal response of pulmonary function to bronchodilators in cystic fibrosis. Pediatr Pulmonol 1990;9:80-85.
2. Aubier M, Viires N, Murciano D, et al. Effects and mechanism of action of terbutaline on diaphragmatic contractility and fatigue. J Appl Physiol 1984;56:922-929.
3. Verdugo P, Johnson NT, Tam PY. Beta-adrenergic stimulation of respiratory ciliary activity. J Appl Physiol 1980;48:868-871.

Jobe: The issue of efficiency of delivery is a major problem that has not been specifically addressed for pediatric and especially for neonatal patients. New equipment will need to be designed if higher efficiencies are to be achieved in small patients. To illustrate the problem, the average nebulizer requires at least 10 L/min of gas to operate. A 1-kg baby being ventilated at 30 breaths/min and at tidal volumes of 10 mL/kg will have a minute volume of 300 mL or about 3% of the aerosol flowrate. Assuming that less than 20% of the inspired aerosol will settle in the distal lungs, less than 1% deposition will occur. We have been working with a prototype nebulizer that will deliver submicronic particles at a flowrate of 2 L/min.[1] New equipment and new strategies will be required before aerosol treatments of infants become efficient or predictable.

1. Lewis J, Ikegami M, Higuch R, Jobe A. Nebulized versus instilled exogenous surfactant in an adult lung injury model (abstract). Clin Res 1991;39:42A.

Rau: I would certainly second that. I think what all the data are showing is that the size of the endotracheal tube and the size of the airway require much smaller particle sizes to deliver adequate doses,[1,2] and we don't have the equipment for that.

1. Cameron D, Clay M, Silverman M. Evaluation of nebulizers for use in neonatal ventilator circuits. Crit Care Med 1990;18:866-870.
2. Flavin M, MacDonald M, Dolovich M, Coates G, O'Brodovich H. Aerosol delivery to the rabbit lung with an infant ventilator. Pediatr Pulmonol 1986;2:35-39.

Jobe: And much smaller flowrates if you want any efficiency at all.

Rau: Right. Exactly.

Carlo: One way to evaluate the efficacy of bronchodilators is to do pulmonary function testing, which is

what has been done in most of the studies you cited. Now that we have techniques that are pretty much clinically accepted, it's something that we should make more of a routine. Patients on bronchodilators should occasionally during the course of the therapy be evaluated to determine the effect of these agents on pulmonary resistance. Obviously, there is still a lot of variability in the results.

Rau: In your opinion, what is the sensitivity of the current pressure-flow systems, the pneumotachograph at the airway with the microcomputer-based monitoring system? What is their sensitivity to detecting or differentiating small airway change from say larger airway? Are they good at that? Dr Carlo? Or anyone for that matter?

Carlo: Maybe Ron Goldberg could comment on this because in Miami they have also done studies comparing different techniques. But, for a long time, we have done pressure and airflow measurements with our own program or hand analysis. I think the computer programs currently available are pretty good—if you collect the data correctly, if you are very careful with prevention of leaks around the mask, and if you're careful about the measurement of esophageal pressure. I believe Drs Gerhardt and Bancalari in Miami have tested some of the commercially available software and hardware and found results that are comparable to those of standard techniques to measure pulmonary function.[1] They have also performed comparisons between static compliance and dynamic compliance with the different techniques.

1. Gerhardt T, Reifenberg L, Duara S, Bancalari E. Comparison of dynamic and static measurements of respiratory mechanics in infants. J Pediatr 1989;114:120-125.

Goldberg: I personally don't have experience testing those measurements. One concern that I have is that most of the studies that you cited showed some positive effect. Even our own showed a fairly dramatic drop in resistance. However, the drop in resistance lasts approximately ½ to 1 hour, which really makes the current drugs ineffective over the long-term. In an interesting study by Brundage and co-workers,[1] ipratropium bromide and salbutamol were used together and appeared to be effective over a 2- to 4-hour period.

1. Brundage KL, Mohsini KG, Froese AB, Fisher JT. Bronchodilator response to ipratropium bromide in infants with bronchopulmonary dysplasia. Am Rev Respir Dis 1990;142:1137-1142.

Rau: I would like to add to that very briefly. That type of result fits exactly with the usual dose-response studies that you see in pharmacology where the duration of response is to some extent a function of dose. If you underdose, you get a shorter response as well as a lower peak response. That could very well be consistent with the fact that we are seriously underdosing these infants—that underdosing is the problem, not that the infants are not responsive to the drug.

Green: With pneumotach and esophageal pressure measurements, we can determine pulmonary resistance. Getting back to your question about large and small airways—I'm not sure how that system would measure or differentiate between resistance in large and small airways. You could get into questions about changes in dynamic compliance, but these systems usually measure dynamic compliance at the respiratory rate of the patient rather than frequency dependence of dynamic compliance, which is the classic indicator of small airways disease in adult pulmonology. And I wonder if Dr Goldberg, or someone else, has a further comment on small versus large airways with infant pulmonary function testing.

Martin: Two drugs have had a major impact on neonatal care—surfactant and corticosteroids. Clearly both of these drugs hold a lot of promise if the techniques for administering aerosolized drugs can be improved. Is there any new information on the use of aerosolized steroids for patients with BPD?

Green: We have used them in some older babies, not babies in the neonatal intensive care unit but in outpatients with bronchopulmonary dysplasia and severe reactive airways disease. We have used nebulized dexamethasone and triamcinolone because those drugs with more favorable pulmonary-to-systemic activity aren't available in this country. My understanding is that preferred agents such as budesonide are available for nebulization in Europe, and we hope they will be available here in a few years.

O'Rourke: In the pediatric intensive care unit, continuous or frequent nebulized $beta_2$-agonists have virtually taken the place of I.V. isoproterenol infusions for status asthmaticus. But studies are needed: At a recent pediatric critical care symposium, more than a 400% difference in $beta_2$-agonist doses was reported.

In addition, while we are concerned about inadequate dosage of $beta_2$-agonists, the potential cardiotoxicity must be addressed. The younger child with normal coronaries can tolerate very high doses, but the 18- to 19-year-old patients who may already have early coronary artery disease may suffer myocardial ischemia at these same doses.

Rau: Good point.

Carlo: Regarding your comment on the use of aerosolized steroids in

patients with BPD, a lot of that work is experimental and results are preliminary.

Rau: One study has shown improvement in patient condition.[1]

1. Maayan C, Itzhaki T, Bar-Yishay E, Gross S, Tal A, Godfrey S. The functional response of infants with persistent wheezing to nebulized beclomethasone dipropionate. Pediatr Pulmonol 1986;2:9-14.

Pierson: Joe, it is clear from your excellent presentation and also from the vigor of our discussion that there's a great need for a consensus about the clinical use of aerosols and also for standards for pursuing research in this area. Just for the information of the group, the American Respiratory Care Foundation and RESPIRATORY CARE Journal next month (December 1990) will convene a consensus conference on the clinical use of aerosols, both diagnostically and therapeutically, in respiratory care—assembling a group, not unlike this, including experts from both Europe and North America, and covering the whole spectrum of research and practice in aerosol therapy in order to try to come as close to consensus as is possible at this particular time. That Conference will be reported in the September 1991 issue of the Journal.

Chest Physiotherapy in the Pediatric Age Group

Jens B Andersen MD and Merete Falk PT

Introduction

In recent years, the efficacy of chest physiotherapy has been questioned.[1-4] Fortunately, the respiratory care community in general has reacted in a professional manner, and a number of controlled clinical trials have been conducted that have been very illuminating.[3,5-8] A number of classic techniques have been abandoned because no benefits have been demonstrated or the techniques have been shown to be hazardous.[9-11] Other respiratory care strategies have been implemented based on solid basic research.[12-14] In this paper we discuss the various regimens and their clinical documentation. If such documentation is not available, we propose a possible pathophysiologic platform, or rationale.

The key word is perception. There are no facts; there is no reality. There is only what is perceived to exist. The crucial question to ask then is: What is the perception of the lung and thorax in general and the lung periphery in particular as it applies to different chest physiotherapy strategies?

Rationale

If we are to address the perception issue, it is important to link structure to function in order to distinguish between winning and losing strategies.

Figure 1 is a well-known model of the lung demonstrating the increase in total surface area that occurs moving from the trachea down the airways to the alveolocapillary membrane. The figure clearly distinguishes between a central zone representing the first 5 to 7 generations of the bronchial tree and a peripheral zone representing the rest of the air-filled portions of the lung. Expiratory flowrate at the airway opening (mouth) is the sum of a large number of smaller flowrates in the lung periphery. Thus, even a high expiratory peak flow (such as occurs during a cough) is associated with low flows in terminal airways.

The two routes of intervention are the airway opening and the chest wall. But, what do we think happens in the central and peripheral lung regions in response to manipulations from outside? Clearly, we must distinguish between techniques that have an effect centrally and techniques that, predominantly, have an effect peripherally. Unfortunately, this is seldom done in dealing with respiratory care strategies.

Classic Chest Physiotherapy

Treatment that can facilitate clearance of excessive secretions and can optimize airway function is considered an important part of prophylactic respiratory care in patients with obstructive pulmonary diseases and in patients in the postoperative period. The principal causes of impaired peripheral ventilation in these conditions are obstruction and collapse of small airways. The aim of therapy is to prevent atelectasis and/or trapping of secretions.[1,2,15,16] Treatment strategies must be modified accordingly.

Percussion

Percussion, a procedure characterized by rhythmic clapping with cupped hands over the affected portion of the lung or the simulation of such movement by the application of a reciprocating

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mechanical device, has no demonstrable beneficial effects[3,5,17-20] and may induce hypoxemia[5,9,10] and worsen large airway function.[3,5,11] The chest wall and lung periphery function as a damping system, and do not allow assaults made to the chest wall to reach the lung parenchyma—at least not in a beneficial way.

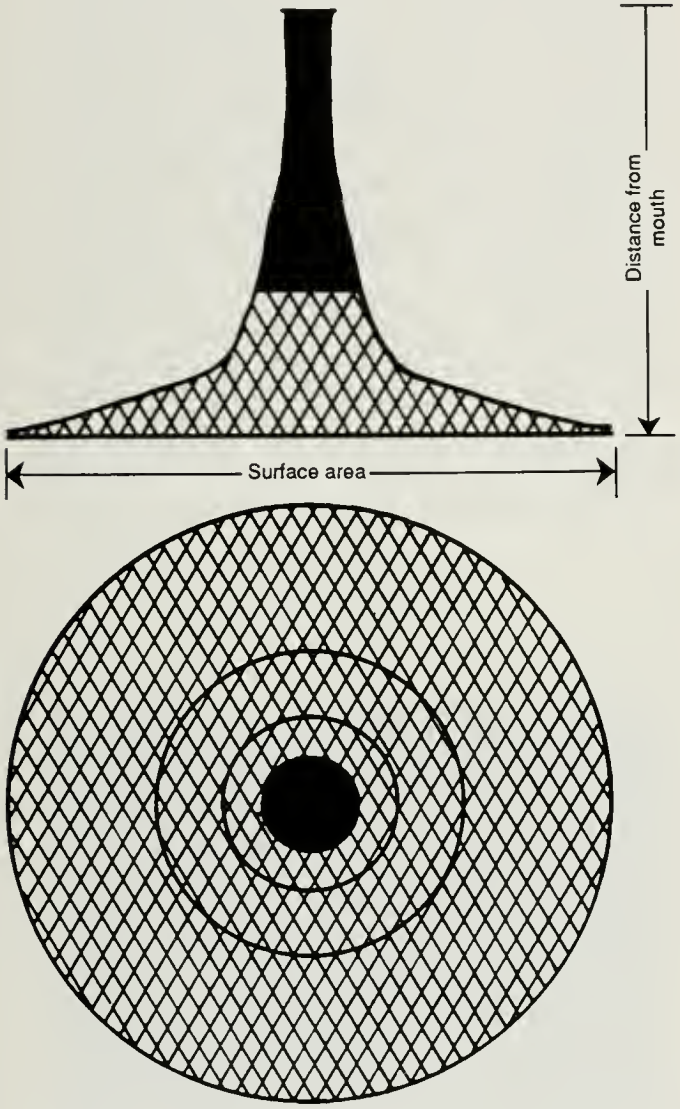

Fig. 1. The 'trumpet' model of the lung demonstrating a central zone (black) and a peripheral zone (hatched).

Postural Drainage

The usefulness of postural drainage (positioning the patient to promote gravity-assisted drainage of the lungs) is purely speculative. The proposed mechanism is that when the affected portion of the lung is placed uppermost with its bronchi dependent, then secretions will follow the law of gravity and 'fall' centrally. The effectiveness of this method for enhancement of bronchial clearance is not striking.[4,6,21,22] Certainly the finding that postural drainage improves sputum production is not universal. Some studies suggest that it does,[6,22-24] and some show that it does not.[5,7,25,26] There can be no doubt that gravity affects lung function, but to take this further and claim that certain drainage positions are helpful for secretion removal seems to be undocumented. This is in spite of the fact that with the subject in the lateral decubitus position the distribution of ventilation can be affected by shifting from costal to diaphragmatic breathing even at resting lung volume (FRC).[27]

Forced Expiration Technique and Cough

The forced expiration technique (FET), controlled diaphragmatic breathing with so-called huffing (a large inspiration followed by a series of short expiratory blasts punctuated by pauses), is only helpful in central airways down to the seventh generation,[4,6,28] but has proven to be a useful strategy to clear that part of the bronchial tree.[29] Unfortunately, nobody has determined whether gradation of expiratory flow (ie, changing expiratory flow) improves the effects of the FET.

Autogenic Drainage

Autogenic drainage is a technique that begins with low-lung-volume breathing, inspiratory breath-holds, and controlled exhalation and progresses to increased inspired volumes and increased expiratory flowrates. It has been claimed to be superior to all other existing techniques,[30] but we believe that the claim has not been adequately documented. To our knowledge, no acceptable controlled clinical trials have demonstrated any beneficial effects whatsoever. Furthermore, the technique is difficult to teach to patients, and it is hard to believe that it can be useful in seriously ill patients.

Breathing Control and Breathing Exercises

Despite the theoretical advantages—improved removal of secretions, improved respiratory muscle strength and endurance, and increased tidal volume and chest-wall motion—spontaneous or induced deep-breathing exercises have not proven adequate to deal with peripheral airway obstruction or collapse.[15,31,32] Again, conceivably, this has to do with the disparity between the true condition within the lung periphery and our perception of it.

Impact on Therapy

The considerations discussed have had great impact on chest physiotherapy in Scandinavia, Europe, and increasingly all over the world. If the area of interest is central airways, cough and/or the forced expiration technique can deal effectively with the problem. If the area of interest is the lung periphery, a solution may be somewhat more difficult. Apparently, chest percussion has no beneficial effects and might be harmful. Postural drainage is not of much help, and breathing control cannot always deal with the problem.

The New Vision

Methods are needed that can open up and recruit the obstructed lung periphery.[8,12,16,33,34] Periodic application of continuous positive airway pressure (CPAP) and positive expiratory pressure (PEP) has been suggested for this purpose.[5,7,13] Application of these modes increases the airway transmural pressure in both the central and the peripheral airways, which conceivably can lead to a dilatation of the bronchial tree. This dilatation might promote inflow of air behind obstructions either through the ordinary bronchial route or through collateral channels and might recruit obstructed or collapsed peripheral lung units. Gas exchange may improve and secretions may be mobilized to more central airways where FET and/or cough effectively can deal with them.

Mechanisms of Action

The most efficient way to improve function of an obstructed airway is to increase the outward pull on the airway by increasing lung volume.[15] In order to more fully understand the implications for therapy, one should consider the lungs not just as 2 balloons attached to airways, but as 300 million balloons each connected to its own airway intercommunicating with other airways and balloons through collateral channels.

Figure 2 demonstrates such an arrangement in the normal lung, in an obstructed region, and in a hyperinflated region. The neighboring regions try to 'help' the region in trouble (ie, in the obstructed case the outward pull increases, and in the hyperinflated case the outward pull decreases).[35,36]

Figure 3 demonstrates the effect of PEP in and surrounding an obstructed region. The increased lung volume of neighboring units increases the outward pull on the obstructed part. Conceivably, reexpansion or recruitment of the obstructed part is enhanced and secretions are forced centrally, where they can be dealt with by cough and/or FET.

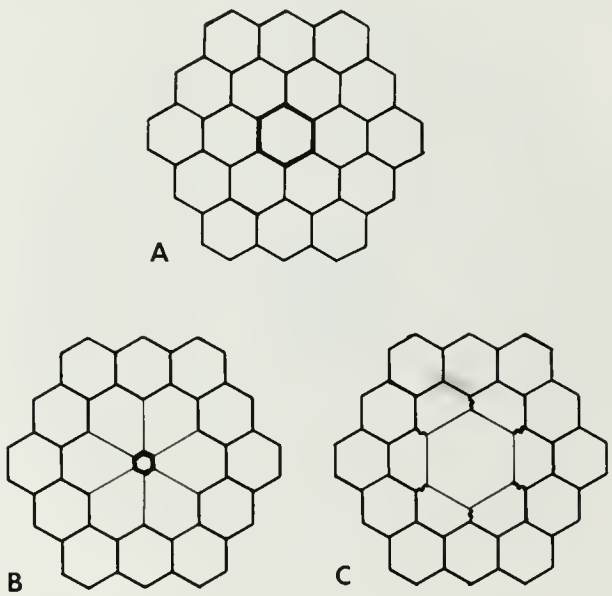

Fig. 2. The lung periphery. A. With normal alveolar volume, the peripheral airway is stabilized by outward pull from surrounding alveolar septa. B. In the obstructed state, the decreased caliber of the airway increases outward pull on adjacent alveolar septa. C. In the hyperinflated state, the increased caliber of the airway decreases outward pull on adjacent alveolar septa.

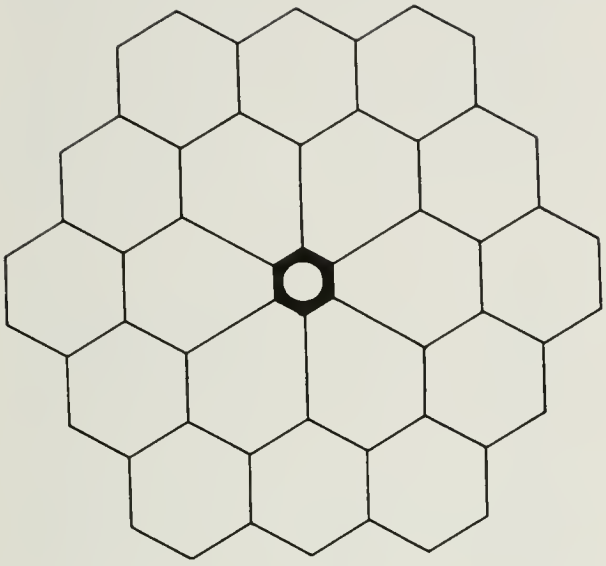

Fig. 3. Effects of PEP applied at the airway opening on an obstructed region of the lung periphery. Increased outward pull from surrounding enlarged alveoli tends to reexpand obstructed alveolus.

Fig. 4. The AMBU PEP-mask system with mask, valve, and resistance caps.

PEP Treatment

The PEP mask system (Ambu Inc, Hanover Md) shown in Figure 4 consists of a face mask and a valve upon which expiratory resistance caps can be mounted. A manometer can be inserted between valve and resistance cap to determine the exact PEP level. The resistance cap is determined for each individual patient to give a steady PEP of 10-20 cm H_2O during the middle part of expiration. Based on my experience with patients, this pressure should be maintained during two minutes of tidal volume breathing through the system.

The appropriate resistance cap is selected as follows: The patient is seated comfortably and holds the mask tightly over nose and mouth. Tidal volume breathing with only slightly active expiration is used. The different caps are tested while the exact PEP level is read from the manometer. The size of the hole in the resistance cap is gradually decreased until the correct PEP level has been identified. Forced and complete expiration should be avoided. This is the reason for using a flow resistor rather than a threshold pressure valve. The patient should keep the lungs expanded and the lung volume up. Treatment is carried out in the sitting position. The patient takes about 10 PEP breaths followed by FET and coughing to bring up secretions mobilized with PEP.[29] The cycle is repeated several times. The frequency and duration of each treatment is adapted to the needs of the individual patient. About 15 minutes, twice a day, is usually recommended when PEP is prescribed as prophylactic treatment during stable pulmonary disease.[5,8] In the postoperative patient, 30 breaths with PEP every hour during the day and a few times during the night have proven useful.[7]

Even small children can use the system but should be supervised during treatment sessions. Correct adjustments of resistance caps and careful instruction and supervision of treatment technique with regular control sessions are mandatory.

Documentation

On the assumption that it is important to increase the amount of sputum expectorated, the immediate and long-term effects of PEP-mask therapy have

been compared with other physiotherapy regimens. We have studied the immediate effects of PEP in cystic fibrosis patients.[5] Controlled sputum sampling, oxygen tensions, and large airway function were used as outcome measures. Furthermore, immediate effects of PEP on both central and peripheral airways have been investigated.[14] The long-term effect of PEP administered as a natural part of chest physiotherapy has been evaluated.[37] Overall, the results demonstrate that both central and peripheral airway function improves during PEP, and oxygen tensions increase both during and following this treatment. During percussion, a substantial and unacceptable decrease in oxygen tension occurs. PEP as a supplement to FET resulted in a greater sputum yield than was obtained with the other techniques. These studies clearly demonstrate that PEP-mask therapy has an effect on obstructed lung periphery, an effect conceivably valuable in chest physiotherapy strategies.

It has been postulated that exercise will accomplish the same effects as does PEP therapy.[38] However, in a randomized controlled study,[39] PEP therapy was more effective in increasing sputum yield and improving small airway function than was exercise.

It is mandatory that studies of efficacy control for number of coughs during a treatment session, that sputum be collected in a consistent manner, and that the treatment sessions be of the same length. Unfortunately this has not always been the case.[24,40]

Long-term treatment of chronic bronchitis with PEP mask and chest physiotherapy was addressed in a controlled study by Christensen et al.[8] The PEP group had significantly less cough and less mucus production. The number of acute exacerbations was calculated from diaries and was lower in the PEP group compared to the control group. In the PEP group, 85% of the patients were free from acute exacerbations during the study period, compared to 48% in the control group. The PEP group used fewer antibiotics and mucolytics. A small but significant increase in FEV_1 occurred in the PEP group and a small decrease in the control group.

In postoperative patients, a variety of methods have been advocated to normalize pulmonary function or to treat postoperative atelectasis.[1,32] Again, CPAP and PEP seem to be of advantage. Periodic CPAP has led to a more rapid normalization of pulmonary function than deep-breathing exercises or incentive spirometry.[41] In the treatment of postoperative atelectasis, periodic CPAP with a face mask and pressures of 15- to 20-cm H_2O has been shown to be superior to ordinary chest physiotherapy.[13] Furthermore, Ricksten et al[7] reported that periodic CPAP and PEP-mask treatments were equally effective in improving gas exchange, normalizing pulmonary function, and preventing atelectasis. Both were more effective than incentive spirometry following upper-abdominal surgery. Clearly, the best chest physiotherapy offered to the surgical patient is early ambulation with its associated normalizing of pulmonary function. Periodic CPAP or the much less cumbersome system of PEP mask should only be considered for high-risk patients (ie, those undergoing upper-abdominal surgery, those with abnormal preoperative pulmonary function or secretions, and elderly patients and obese patients).

In Conclusion

Many older or classic chest physiotherapy strategies have not been able to stand the challenge of time or controlled clinical trials. Percussion and classic postural drainage are among these. The effectiveness of the forced expiration technique and coughing is well documented—but only effective in central airways. To overcome problems in the lung periphery, other methods are indicated. Periodic CPAP or the much easier PEP-mask therapy is attracting increasing interest, and has already proven effective in clinical controlled trials in patients with postoperative pulmonary problems, cystic fibrosis, and chronic bronchitis. Whether such approaches will change the natural history of these diseases is, by and large, unknown, but the issue must be addressed in controlled studies. In our part of the world, positive expiratory pressure was first used by Bunnell in 1912 during thoracic surgery.[42] In 1935, Barach[43] used it in obstructive diseases, and in 1936 Poulton[44] used it for pulmonary edema. My group introduced periodic CPAP in 1980[13] and the PEP mask was introduced by Falk et al in 1984.[5]

It may be that the origin of PEP dates back to classical Chinese history in the period preceding the

Han Dynasty. In the *Tseen Han Sho*, written around 30 BC and translated by Wylie in 1881,[45] a mountain trip from the western regions to the Hindu Kush in Afghanistan is described. Travelers experience acute mountain sickness crossing the Great Headache Mountain and the Little Headache Mountain. It was suggested that the condition improved by breathing out through cloths—low-dose PEP!

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Andersen Discussion

Hess: My question in looking at these devices (with which I have been intrigued) relates to your design of the PEP (positive end-expiratory) mask. Why did you choose to use a fixed expiratory resistance rather than the threshold-type valve more commonly used to produce PEEP and CPAP? It seems to me that there might be more benefit to using a 7.5 cm-PEEP valve, for example, than in using a fixed resistance.

Andersen: I agree with you, and I must admit it was one of my major complaints from the beginning. As you know, Denmark is a rather poor country, and if you had to put on a valve with a threshold-type resistance, then that would increase dramatically the cost of the equipment. That was one argument. The other argument, which I must admit I didn't buy in the beginning, was the fact that some of our patient-care staff told us that it was useful that the resistance depends on the expiratory flow of the patient. If patients have some trouble getting the secretions up, then they increase their expiratory flow in order to increase the PEP pressure. So they sort of work against the resistance in order to get a higher pressure. And I must admit that makes sense to me.

Hess: Is it not also possible that the patient could adjust their ventilatory pattern so they would get very little or no expiratory pressure?

Andersen: That brings up the question How do you instruct the patient to use these devices properly? The way that is done is that you measure the pressure with a manometer, instruct them absolutely correctly on how to use it, and then determine on the manometer that the pressure of 15-20 cm H_2O is reached constantly with only a slight expiration during 2 minutes of normal tidal breathing. If you do that, then those working with patients tell me that patient compliance in terms of use is pretty high, and if when they next work with the patient—1 hour or two weeks later—they find out that the PEP pressure actually is pretty constant at the level desired. Certainly, I agree that we will all change our ventilatory pattern when we put on a face mask or use a resistor, but that should be matched to each individual patient at the first visit.

Mathews: At the 1989 World Congress on Home Care held in Rome, Italy, there were several papers on PEP mask—most of them from France.[1-4] From my recollection, those papers confirm what you were saying—they showed a definite increase in functional activity of the patient and increased compliance with the treatment regimen using those PEP masks.

1. Marrone O. CPAP in treatment of obstructive sleep apnea syndrome (abstract). Rome: World Congress on Home Care, 1989.

2. Krieger J. Long-term treatment with CPAV in obstructive sleep apnea syndrome (abstract). Rome: World Congress on Home Care. 1989.
3. Leger P. Technical support and new devices for respiratory home care (abstract). Rome: World Congress on Home Care, 1989.
4. Newton-John H. Nasal mask ventilation at home: An experience of 11 patients (abstract). Rome: World Congress on Home Care, 1989.

Andersen: One thing that I think is important is the issue of patient cooperation. I have been told and have seen that PEP masks can be used successfully in those patients who do not cooperate.

Mathews: To follow up on that—part of the reason for improved compliance might be the lack of need for a lot of peripheral equipment. The PEP masks are much lighter and easier to use than the CPAP devices. That may foster increased compliance.

Green: Do children under 2 or 3 years of age receive no therapy or do they receive chest physiotherapy in the conventional way?

Andersen: Mahlmeister et al[1] presented an abstract at the 1990 AARC Annual Convention in New Orleans describing the case of a 3½-year-old girl for whom PEP-mask therapy proved more efficacious than postural drainage and percussion. These authors also stated that they employed PEP-mask therapy in a number of other pediatric patients (age 3½-14 y) and observed greater sputum production than had been previously observed with postural drainage and percussion. We have used it in patients as young as 2½ years.

1. Mahlmeister M, Hoffman G, Fifer L. Positive expiratory pressure (PEP) mask therapy as a bronchial hygiene technique (abstract). Respir Care 1990;35:1090-1091.

Goldberg: Just a note of caution regarding chest physiotherapy with small, premature babies, especially the baby with hyaline membrane disease who's early into his disease. I think we just have to be careful in any routine type of physiotherapy for these children. I don't think it is indicated. Suctioning, if there seems to be an indication, is appropriate. But I think at least in the past we used to have this tradition of suctioning every 4 hours or 2 hours, whatever. I think the side effects in terms of increased intracranial pressure and possibly aggravating intraventricular hemorrhage really makes those activities less desirable in the premature infants.

Andersen: I agree completely with you. I think the most important part about this thing certainly is that treatment should always be individualized. That's one thing. The other thing is that I am not an expert on neonates. To my knowledge, periodic PEP or CPAP has not been used in neonates.

Goldberg: Can you comment on the use of vibration during chest physiotherapy in premature infants or children with BPD?

Andersen: When you vibrate these children something certainly happens. But, I must admit, the only thing it seems to me that happens is that it might shake the central airways because you shake the whole child. When you do that then you may be able to induce a cough. I must admit that I thought that the difference in the mechanical compliance of the chest wall made a difference. But there are studies demonstrating that distortion of even the pleural surface cannot be detected at a distance of a few alveoli.[1]

1. West JB. Regional differences in the lung. New York: Academic Press, 1977:281-322.

Barnes: Would you comment on whether you think there are advantages to using mechanical or pneumatic percussors rather than your hands.

Andersen: I don't think so. People[1] who have tried to look into this and tried to explain how it works have come up with something about the frequency on which the percussor works—stating that if it was close to the resonance frequency of lung/thorax or the ciliary beating frequency that might be good. The notion then is that the frequency certainly will change with and within lung disease. As far as I can see, no clinical scientific evidence supports any of these percussion methods. But, as I suggested, there are data demonstrating that in rather small proportions of all patients it might actually be harmful.

1. King M, Phillips DM, Gross D, Vartian V, Chang HK, Zidulka A. Enhanced tracheal mucus clearance with high frequency chest wall compression. Am Rev Respir Dis 1983;128:511-515.

Barnes: With adults, some studies[1-4] have shown that if patients aren't producing a minimum of 30 mL/day of sputum, chest physiotherapy does no good. Are there any studies for children or infants that show similar kinds of results?

1. Newton DAG, Stephenson A. Effect of physiotherapy on pulmonary function. Lancet 1978;2:228-230.
2. Newton DAG, Bevans HG. Physiotherapy and intermittent positive pressure ventilation of chronic bronchitis. Br Med J 1978;2:1525-1528.
3. May DB, Munt PW. Physiological effects of chest percussion and postural drainage in patients with stable bronchitis. Chest 1979;75:29-32.
4. Mohsenifar Z, Rosenberg N, Goldberg HS, Koerner SK. Mechanical vibration and conventional chest physiotherapy in outpatients with

stable chronic obstructive lung disease. Chest 1985;87:483-485.

Andersen: Not to my knowledge.

Orenstein: This is a comment rather than a question—partly to second your word of caution about the literature being pretty empty in terms of good comparative studies. I think we have to interpret studies that compare how things are nowadays when we're using PEP masks compared to how they were ancient-history-wise when we didn't use PEP. We have to be very cautious about that. For example, in Denmark, as you are well aware, in the last 10 years, in addition to using PEP masks they have also hospitalized all CF patients for intravenous antibiotic therapy 2 weeks out of every 3 months. One might make the case that this may have made a bigger difference in terms of improving pulmonary function and overall lung health than a particular form of chest physiotherapy.

Andersen: I agree. Pedersen has documented that.[1] The reason I showed the slide on pulmonary function was that some claim that lung function will deteriorate if you do not use percussion.[2]

1. Pedersen SS, Jensen T, Heiby N, Koch U, Flensborg EW. Management of *Pseudomonas aeruginosa* lung infection in Danish cystic fibrosis patients. Acta Paediatr Scand 1987;76:122-130.
2. Reismann JJ, Rivington-Law B, Corey M, et al. Role of conventional physiotherapy in cystic fibrosis. J Pediatr 1988;113:632-636.

Assessment of the Pediatric Airway by Flexible Bronchoscopy

Christopher G Green MD

Introduction

Flexible bronchoscopy was introduced by Ikeda[1] in 1966. The technique was initially used only in adults due to the diameter of the instruments. Since the introduction of the first pediatric bronchoscope in 1978,[2] the use of flexible bronchoscopy in infants and children has grown steadily. Flexible bronchoscopy is an exceptional diagnostic tool and has several therapeutic uses as well. In this paper I discuss the technology of fiberoptic imaging, the equipment used in pediatric bronchoscopy, indications for flexible bronchoscopy (including its use in the neonatal intensive care unit), and anesthetic-sedative techniques. Flexible and rigid bronchoscopy are compared because both techniques are necessary for the comprehensive management of children with airway problems.

Fiberoptic Technology

Light transmission through a fiberoptic cable depends upon internal reflection of light down the length of individual glass fibers, as shown in Figure 1. Introduced in 1957 by Curtiss and Hirschowitz,[3] modern fiberoptic technology uses glass fibers clad with a layer of a different glass. Light passing into the end of a plain glass fiber will undergo internal reflection as it passes down the length of the fiber, but a large amount of the light may be lost via refraction through the wall of the fiber. Light entering the fiber nearly parallel to the fiber's length will undergo mostly internal reflection and emerge from the other end of the fiber. Light entering at a greater angle undergoes greater loss by refraction. If the fibers are clad with glass of a lower refractive index, refractive losses can be reduced to nearly zero for light that strikes the core-cladding interface at an angle of incidence (as measured from normal) greater than the critical angle. (The critical angle is determined by the refractive indices of the core and cladding glasses.) This approach assures excellent transmission of light through a clad fiber, but each fiber provides only a tiny dot of light.

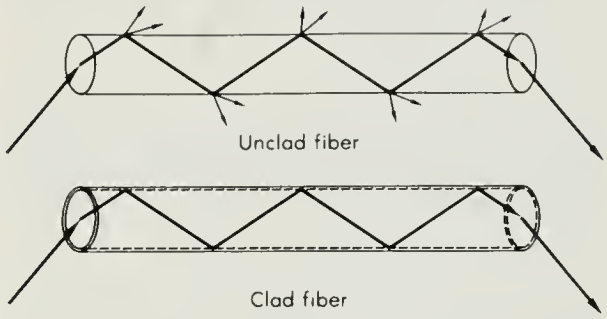

Fig. 1. An unclad fiber with a contaminated surface loses light throughout its length. Cladding protects the interface surface and increases transmission efficiency. (Reprinted, with permission, from Reference 3.)

Image production with fiberoptics requires a coherent bundle of thousands of clad fibers each about 8 μm in diameter. Figure 2 shows how the clad fibers are arranged in a bundle. The term

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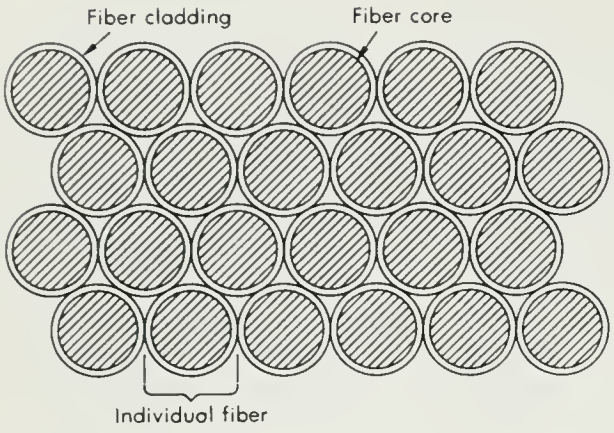

Fig. 2. Individual fibers are grouped into a bundle in a honeycomb pattern. Only the light falling on the core glass (shaded area) is transmitted. (Reprinted, with permission, from Reference 3.)

coherent means that the arrangement of individual fibers at one end of the bundle is exactly duplicated at the other end of the bundle. As shown in Figure 3, an image can then be transmitted from one end of the bundle to the other without distortion. The image is composed of thousands of dots of light with each fiber producing one dot. If the bundle

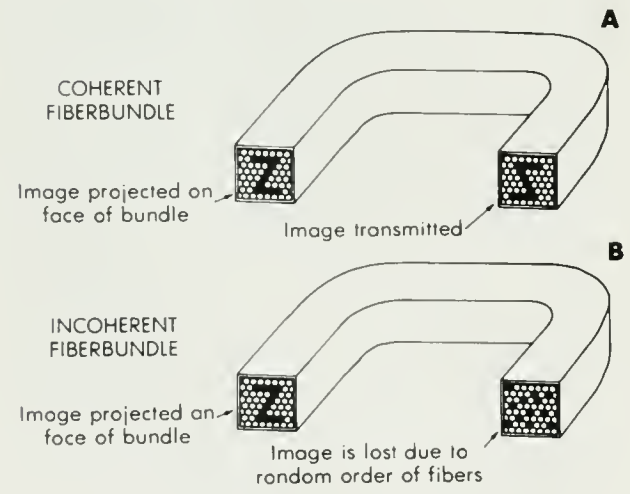

Fig. 3. In a coherent fiber bundle, the arrangement of fibers in one end of the bundle exactly matches the arrangement in the opposite bundle face (A). An incoherent bundle exhibits no correlation between the fiber arrangements in the two bundle faces (B). (Reprinted, with permission, from Reference 3.)

is not coherent, it will not transmit an image but will still transmit light. Noncoherent bundles called light guides are used to carry light for illumination from the light source, through the bronchoscope, and into the patient.

Recently, some larger endoscopes have incorporated a charge-coupled device (CCD) at the tip of the scope. The CCD is a solid-state electronic device, used in many video cameras, that converts the image into an electronic signal carried through wires to a video display. This type of instrument uses fiberoptics to carry light into the patient, but fiberoptics are not used in the imaging process. In the future, more endoscopic imaging will be performed by CCDs. Currently (1991), CCDs are not small enough to be used in pediatric bronchoscopes.

Equipment and Facilities for Fiberoptic Bronchoscopy

The typical pediatric flexible bronchoscope (FBS) has a 3.5- to 3.6-mm outer diameter (OD) with a 1.2-mm suction channel and 160° of distal flexion. This instrument can be used for most pediatric examinations, even of premature infants weighing less than 1,000 g. Smaller bronchoscopes (2.7-mm OD and 2.2-mm OD) have similar distal flexion but no suction channel. These ultrathin bronchoscopes are very useful for examination through indwelling tracheostomy or endotracheal tubes, and may also be used to guide the intubation of small infants. Even smaller fiberoptic imaging devices (1.8-mm OD and 1.1-mm OD) are available, but have no suction channel and no distal flexion. Their use is limited to patients with artificial airways. Applications include the determination of endotracheal tube placement and evaluation of the distal trachea and main-stem bronchi for mucus plugging, granulomas, or inflammation.[4-6] Slim, adult-sized bronchoscopes (4.9-mm OD with a 2.0-mm suction channel) may be used with older children if transbronchial biopsy is planned.[7]

Flexible nasopharyngoscopes with outside diameters of 3.5 mm are available. These are useful for rhinoscopy, nasopharyngoscopy, and laryngoscopy, but they have no suction capabilities and are too short for bronchoscopy. Also, intubation

bronchoscopes with outside diameters of 3.5 mm are marketed. These are similar to the standard pediatric FBSs, but are stiffer to facilitate the use of the instrument as an endotracheal tube guide.

Light sources for flexible bronchoscopy vary in light production. Brighter light sources are superior for pediatric applications because of the small fiberoptic bundles used in the pediatric instruments.

A variety of imaging systems are available for use with FBSs, including conventional 35-mm, Polaroid, and video cameras. The quality of video cameras continues to improve, and such cameras are preferred for pediatric bronchoscopy because of the importance of dynamic findings in the airway.

Other equipment needed for pediatric bronchoscopy is listed in Table 1. The availability of appropriate monitoring and resuscitation equipment is as important as the availability of the bronchoscope. Supplies for cleaning and disinfecting the bronchoscope are also necessary for any bronchoscopy suite.

Table 1. Equipment and Supplies for Pediatric Flexible Bronchoscopy

Flexible bronchoscopes	Intravenous supplies
Light source	Sedative agents
Video camera	Lidocaine for topical anesthesia
Adjustable examination table	Naloxone
Oxygen outlets (2)	Resuscitator bags and masks of appropriate size
Suction outlets (2)	Tracheostomy and endotracheal tubes
Electrocardiographic monitor	Resuscitation cart
Pulse oximeter	Cleaning supplies

Bronchoscopy Assistants

Pediatric flexible bronchoscopy with sedation is carried out in the ideal situation by a three-person team: the bronchoscopist and two assistants. One assistant administers the sedation and the topical anesthetic and helps with the equipment. The other assistant carries out visual monitoring of the patient, talks soothingly to the patient, and stabilizes the patient's head in the midline position. The second assistant should not be holding down a struggling patient during the procedure; such a patient is inadequately sedated, and bronchoscopy should not be performed under such circumstances. Good communication among team members and consistent, experienced assistants help make bronchoscopies smoother and safer.

Monitoring

The four important aspects of monitoring patients are (1) adequate planning for monitoring during the procedure, (2) visual and aural monitoring, (3) electrocardiographic monitoring, and (4) monitoring by pulse oximetry. The American Academy of Pediatrics has published guidelines for sedation in pediatric patients,[8] that emphasize the importance of adequate personnel and monitoring. They also clearly state that sedated patients should not be left unattended and imply that monitoring should continue after completion of the procedure until the patient is awake and has returned to the presedation level of responsiveness.

Planning for a pediatric flexible bronchoscopy includes planning the monitoring. Although critically ill patients are best examined in the intensive care unit where appropriate invasive monitoring is available, most patients can be examined in the endoscopy suite where noninvasive monitoring is available. Limited examinations (such as rhinoscopy and nasopharyngoscopy) can be carried out safely on older patients in the office with only topical anesthesia and without electronic monitoring.[9]

Visual and aural monitoring are of great importance during flexible bronchoscopy. Observation of the child's color, chest-wall movement, and breath sounds assessed with or without the stethoscope, provide immediate assessment of the patient. For example, a patient with increasing snoring, poor breath sounds, or poor chest-wall movement should not receive further sedation. The responsibility for visual monitoring should be assumed by an assistant. The bronchoscopist must concentrate on the airway anatomy during the examination, but should be aware of the patient's physiologic status.

Electrocardiographic monitoring may reveal tachycardia in stressed patients or bradycardia due to hypoxemia or vagal stimulation. We have rarely noted ventricular and atrial dysrhythmias.

Pulse oximetry is widely used in operating rooms and intensive care units. Despite possible problems with inaccurate readings due to motion artifact, oximetry is a useful early warning device for arterial desaturation. Although supplemental oxygen is not routinely given during pediatric flexible bronchoscopy, it should be administered if patients desaturate. The bronchoscopist should be alerted to the fact that the bronchoscopy and/or the sedation has caused a physiologic perturbation. The bronchoscopist must realize that supplying supplemental oxygen does not assure adequate ventilation and that ventilation is assessed by breath sounds and chest-wall movement.

Indications and Contraindications

Table 2 lists indications for flexible bronchoscopy. The decision to perform bronchoscopy must always be made specifically for the particular patient. For example, the child presenting with uncomplicated croup will not benefit from flexible bronchoscopy, but for a patient who has experienced five or six episodes of croup, bronchoscopy becomes an important part of evaluation. Most cases of chronic cough can be evaluated and adequately treated without bronchoscopy, but in selected cases bronchoscopy can provide a definitive diagnosis.[10] Even a bronchoscopy with only normal findings can be very helpful by excluding certain diagnoses and thereby allaying anxiety in the patient and family.

Table 2. Indications for Flexible Bronchoscopy

Unexplained stridor	Unexplained wheezing
Recurrent pneumonia	Persistent pneumonia
Persistent atelectasis	Hemoptysis
Unexplained cough	Suspected airway compression
Tracheostomy evaluation	Bronchograms
Suspected tracheoesophageal fistula	Diagnosis of pulmonary infiltrates (bronchoalveolar lavage)
Aid to intubation	

In the most general sense, flexible bronchoscopy is indicated when the potential benefits of the procedure outweigh the risks. When the opposite is true, the procedure is contraindicated. Relative contraindications include severe bleeding and the need to pass the instrument beyond a severe airway stenosis. In cases of suspected epiglottitis, intrabronchial foreign body, or massive hemoptysis, bronchoscopy is needed but, as will be discussed, rigid bronchoscopy is indicated.

Anesthetic-Sedative Techniques

A comprehensive approach to sedation of pediatric patients for flexible bronchoscopy includes (1) control of the ambiance of the bronchoscopy suite, (2) topical anesthesia of the airway, and (3) pharmacologic sedation of the patient.

The ambiance or mood in the bronchoscopy suite is of great importance in maximizing patient comfort and minimizing the need for sedation.[11] Bronchoscopists and their assistants should make every attempt to minimize the child's fear of the new situation. The bronchoscopy suite should be fully prepared before the patient is brought into the room. An assistant talks soothingly to the child during the sedation and the procedure. This approach can even include formal hypnotic induction.[11] The lights in the room are turned down, leaving adequate light for assessing the patient's skin color. Dialogue in the suite is confined to discussion of the patient. A low, relaxed tone of voice is used, and words such as hurt, pain, cough, and bleeding are avoided. The flow of information in the room should be controlled to minimize the patient's anxiety.

Topical anesthesia of the airways is important in all pediatric flexible bronchoscopies. A possible exception to this rule is the examination in which the bronchoscope is confined to an artificial airway. Topical anesthesia of the nose can be achieved with 2% lidocaine solution[12] or with lidocaine jelly[13] applied to the naris. The distal few centimeters of the bronchoscope are coated with lidocaine jelly, and the bronchoscope is then passed through the nasal airway. The oral route is almost never used in pediatrics because of the danger posed to the bronchoscope by the child's teeth. When the nasopharynx is reached, subsequent anesthesia is achieved by the 'spray-as-you-go' method. Aliquots

of 0.5 to 1.0 mL of 2% lidocaine solution are sprayed onto the airway mucosa. After allowing a minute for the lidocaine to take effect, the bronchoscope is advanced and further lidocaine sprayed on the more distal airways.

Topical application of lidocaine results in rapid systemic absorption from the lower airway mucosa and slower absorption of any swallowed drug. The maximum absorbed dose should be limited to 7 mg/kg.[12] Lidocaine toxicity has been documented in children,[14] and such toxicity may be manifested as seizures, tremulousness, or excitement. Therapeutic levels of lidocaine can be reached after topical application of lidocaine to the airways.[15] Some bronchoscopists prefer to use 1% lidocaine in smaller infants because this allows a larger volume of the drug to be used.

The sedation needed for pediatric bronchoscopy is variable, depending upon the age, maturity, medical status of the patient, and extent of the procedure. Cooperative teenagers and older children can be examined with no sedation or after 1 mg/kg or less of intravenous meperidine. Younger children may require 2-2.5 mg/kg of intravenous meperidine. Neonates require less sedation per kilogram of body weight; in small neonates, no sedation is needed. The intravenous route of sedation is preferred because it allows the sedative dose to be titrated to achieve adequate but not excessive sedation. The goal of sedation for pediatric flexible bronchoscopy is to maintain physiologic stability and patient comfort during the procedure.

Opiates are widely used in the sedation of children. Meperidine (1-2.5 mg/kg I.V.), morphine (0.1-0.2 mg/kg I.V.), or fentanyl (1-2 μg/kg I.V.) may be administered. A common, initial dose of meperidine is 1 mg/kg I.V., with additional but usually smaller doses titrated to achieve the desired effect.

Benzodiazepines are often used in combination with narcotic agents. Midazolam (0.03 mg/kg I.V.) is an effective amnestic agent. Although this drug has not yet been approved for use in children, it is widely used in intensive care units and for pediatric endoscopies. Some children become disoriented when given benzodiazepines; therefore, these agents are not usually used as the sole sedative agent for pediatric flexible bronchoscopies.

Occasionally, methohexital, a short-acting barbiturate, may be used as an adjunct in achieving adequate sedation. We have found that when given after meperidine, the methohexital dose should be 0.5-1.0 mg/kg and should be administered over about 30 seconds. Higher doses or rapid administration may lead to apnea.

Sometimes combinations of sedative agents are used in pediatrics. Meperidine and midazolam are combined commonly.[16] A combination of meperidine with promethazine and chlorpromazine (MPC) has been widely used in children. This combination results in prolonged sedation and has been associated with respiratory depression.[17] If MPC is used, prolonged monitoring of the patient is essential.

Shelley et al[18] have discussed the effects of an ideal sedative agent including analgesia, amnesia, and anxiolysis without side effects. In addition, the ideal agent is reversible. Narcotic agents can be reversed with naloxone, and the effects of benzodiazepines can be reversed with flumazenil, but this agent is not yet available in the United States.[18] Both narcotics and benzodiazepines have side effects. Neither class of drugs provides analgesia, amnesia, and anxiolysis. Because the ideal sedative is not available, endoscopists must choose an agent or combination of agents that is best for the particular procedure and patient.

Endoscopists and their assistants should realize that sedation in young children is much different from sedation in adults. Adults usually tolerate bronchoscopy with conscious sedation, whereas young children often require deep sedation. Flexible bronchoscopy should not be performed when it is necessary to restrain the struggling child. In this situation, a good examination is impossible and the experience is unpleasant for the patient, the assistants, and the bronchoscopist. If the child struggles through an initial bronchoscopic procedure, any subsequent procedure will be much more difficult.

Technique of Examination

After adequate sedation and topical anesthesia of the nasal airway have been achieved, the bronchoscope is passed into the nose. The nasal airway, pharynx, larynx, trachea, and bronchi are subsequently examined after further application of

topical lidocaine. Both static and dynamic findings are noted. If one uses the 3.5-mm bronchoscope, even infants under 1,000 grams can be examined. In premature infants, adequate spontaneous ventilation may not be possible once the bronchoscope is past the vocal cords. In such cases, after a 30- to 45-second examination of the lower airways, the bronchoscope is withdrawn above the vocal cords so the patient can breathe.

If indicated, bronchoalveolar lavage (BAL) may be carried out even in small infants. The tip of the bronchoscope is gently wedged in a bronchus. Aliquots of normal saline are instilled into the distal airways (usually 10 mL, but less in infants). Gentle aspiration after each aliquot returns 20-30% of the first aliquot and over 50% of subsequent aliquots. The lavage fluid is cultured, and appropriate cytologic examinations are carried out. The efficacy of this technique in the diagnosis of pulmonary infections in immunocompromised patients is well-established.[19-23] Other uses for BAL include aiding the diagnosis of pulmonary aspiration or pulmonary hemosiderosis. Large-volume lavage has been used in the treatment of pulmonary alveolar proteinosis.[24] After the examination, the patient is monitored until he or she is awake and is tolerating oral intake (usually only 1 to 2 hours when intravenous meperidine is used as the sedative agent).

Care and Cleaning of Flexible Bronchoscopes

Flexible bronchoscopes are relatively fragile instruments, but when used with care they will last for years without repairs. To avoid damaging the fiberoptic bundles in the bronchoscope, the insertion tube and light guide should not be kinked, forced into a small radius of curvature, or crushed. Impact with a hard surface may break the lenses in the insertion tube. Using the bronchoscope as a guide for intubation can be particularly hard on the instrument and should be done with great care.

Flexible bronchoscopes are best stored with the insertion tube hanging vertically. If the insertion tube is curved during storage, it will eventually tend to curve to one side during use.

Most currently marketed bronchoscopes are immersible, but many nonimmersible bronchoscopes are still in use. Disinfection of the outside of the older, nonimmersible instruments requires ethylene oxide sterilization; therefore, immersible bronchoscopes are preferred. The details of cleaning and disinfection will vary, depending upon the instrument. Only some general principles will be discussed here.

After use, the bronchoscope must be carefully cleaned of all blood and secretions. This includes a meticulous cleaning of the exterior of the bronchoscope and the suction channel. After cleaning, the instrument is disinfected. Currently, many institutions disinfect by immersion in 2% glutaraldehyde for 20 minutes. Subsequently, the bronchoscope is rinsed in sterile water and carefully air-dried before storage. Because microorganisms can grow in a moist environment, the suction channel of the bronchoscope must be carefully dried. Rinsing the suction channel with 70% alcohol facilitates drying. Flexible bronchoscopes may be gas sterilized, but immersible bronchoscopes must be properly vented before gas sterilization. Autoclaving at high temperatures melts FBSs.

Infection control in the endoscopy suite is of great importance. Detailed guidelines published elsewhere[25] cover care of equipment, the environment, and the protection of personnel. Transmission of infection between patients by an inadequately disinfected bronchoscope has been documented.[26] Transmission of infection from a patient to the endoscopy staff is also possible, and appropriate precautions should be taken.

Risks and Complications

The complications of flexible bronchoscopy in a series of over 1,000 procedures have been described by Wood.[11] Other authors have confirmed the low incidence of complications in smaller series of procedures.[27-29] One death following flexible bronchoscopy, in a patient with significant lung disease and pulmonary hypertension, has been reported.[30] The incidence of complications in several series is summarized in Table 3.

Informed consent must be obtained before flexible bronchoscopy is performed. Obtaining consent includes discussing with the patient and guardian the risks of the procedure, which vary depending upon the patient; however, three possible risks should be discussed in all cases. First, a small chance

Table 3. Complications of Flexible Fiberoptic Bronchoscopy in Pediatric Patients

Series	Wood[11]	Green*	Fitzpatrick[27]	Fan[28]	Nussbaum[29]	TOTALS
Number of procedures	1,095	415	129	104	96	1,839
Total number of complications	32	19	3	3	8	65
Major Complications						9
Lung abscess	1	—	—	—	—	
Pneumothorax	2	1	—	—	—	
Laryngospasm	1	1	—	—	—	
Respiratory depression from sedation	—	3	—	—	—	
Minor Complications						56
Transient bradycardia	13	—	1	2	—	
Transient laryngospasm	2	—	—	—	—	
Epistaxis	8	8	—	1	6	
Hemoptysis (≤ 10 mL)	—	—	2	—	—	
Anesthetic complications	5	—	—	—	—	
Transient stridor	—	—	—	—	2	
Atelectasis	—	1	—	—	—	
Transient cyanosis	—	4	—	—	—	
Scant bleeding from granulation tissue	—	1	—	—	—	

*Unpublished observations.

of epistaxis exists (usually only a few drops of blood are lost). Second, adverse or allergic reactions are possible due to topical anesthesia or sedation. Finally, hypoventilation may occur due to sedation and/or airway obstruction by the bronchoscope. In an older patient undergoing transbronchial biopsy, hemoptysis and pneumothorax are also risks.

Flexible versus Rigid Bronchoscopy

Anyone involved with flexible bronchoscopy should have some knowledge of rigid bronchoscopy. The two approaches complement each other. In some circumstances, one approach is clearly superior; whereas, in other cases either approach can be used. Occasionally, both instruments are utilized during an examination.[31] A recent review[32] compares the two approaches in great detail.

Patients usually breathe around the FBS. Although oxygen can be delivered through the suction channel of the instrument, this does not assure adequate ventilation. Nutman et al[33] have described a system that allows ventilation of small infants through the 1.2-mm suction channel of the pediatric FBS. Currently, the use of this system is not widespread, and in my experience such a system is rarely needed.

Instrumentation for the 3.5-mm FBS is limited to an unprotected brush, although a laser fiber has been used through the suction channel.[34] Development of a protected brush and a biopsy forceps for this instrument is under way (RE Wood, personal communication, 1990). Several forceps, baskets, biopsy needles, and laser fibers are available for use with adult FBSs.

The rigid bronchoscope is a hollow, stainless-steel tube that is passed into the lower airway and, with proper positioning of the patient, may be advanced into either main-stem bronchus. The smallest rigid bronchoscope has a 4.0-mm OD with a 2.5-mm internal diameter (ID). Larger instruments are available in 0.5-mm-ID increments. Rigid bronchoscopes are referred to by their ID, whereas FBSs are measured by their outside diameters. During rigid bronchoscopy, the patient is under

general anesthesia, and ventilation can be controlled by the anesthesiologist through the bronchoscope. Portions of many procedures are carried out under apneic conditions because large forceps or telescopes may obstruct the lumen of the bronchoscope and, therefore, preclude ventilation. A variety of forceps, scissors, suction apparatus, and spatulas, are available for use during endoscopic surgery and foreign body removal.

The optics of FBSs have steadily improved, and image quality is excellent. Imaging through the rigid bronchoscope alone is similar to looking through a small pipe. However, the glass-rod telescopes used with rigid bronchoscopes provide superb images unmatched by any fiberoptic system.

In contrast to flexible bronchoscopy, which can be performed with topical anesthesia of the airways and sedation, rigid bronchoscopy requires general anesthesia. Thus, rigid bronchoscopy usually involves admission to the hospital on a day-care basis, whereas flexible bronchoscopy can be carried out on an outpatient basis. The cost of a flexible bronchoscopy procedure in our institution is about one third the cost of rigid bronchoscopy. This difference is due to operating room and recovery room charges and anesthesiology fees.

Critically ill patients on ventilators can undergo diagnostic flexible bronchoscopy in the intensive care unit. With the available 2.2-mm FBS, even neonates with 2.5-mm-ID endotracheal tubes can be examined. Rigid bronchoscopy usually requires moving the patient to the operating room, where he or she is extubated, intubated with the rigid bronchoscope, and, after the examination, reintubated with an endotracheal tube. Therefore, flexible bronchoscopy is preferable to rigid bronchoscopy in most critically ill pediatric patients. When patients require a wider range of instrumentation than is possible with the FBS, a rigid bronchoscopy is indicated.

In certain clinical situations, flexible bronchoscopy is superior to rigid bronchoscopy; whereas with other problems, rigid bronchoscopy is indicated. Examination of the nasal and pharyngeal airways is easily carried out with the FBS; whereas the rigid bronchoscope is not used to examine these areas. Flexible endoscopy is usually the preferred approach for upper-airway diagnostic examinations. Rigid endoscopic equipment is available for laryngoscopy and endoscopic sinus surgery—examinations that involve general anesthesia.

Patients with some types of abnormal airways (Table 4) can only be examined by flexible bronchoscopy. For example, micrognathia may preclude access to the airway with the rigid bronchoscope, but flexible bronchoscopy in such cases should be uncomplicated.

Table 4. Clinical Situations in which Flexible Bronchoscopy May Be the Only Approach to Airway Endoscopy

Micrognathia
Facial burns
Unstable cervical spine
Macroglossia
Cystic hygroma
Severe kyphoscoliosis
Mandibular fractures

Flexible bronchoscopy excels for the examination of distal bronchi. During rigid endoscopy, examination can be carried only to the segmental level (or higher). In flexible bronchoscopy, examination of the segmental anatomy is routine and, in many cases, examination of more distal airways is easily accomplished. The depth achieved with the FBS depends upon the size of the bronchoscope, the size of the patient, and the area of the lung being examined. Because of limitations to the flexion of the distal tip of the bronchoscope and the radius of curvature near the tip, examination of the upper lobes in children is more limited in extent than is examination of the lingula, middle lobe, or lower lobes.

Airway dynamics, the movements of the airway during the respiratory cycle, can be optimally evaluated with the FBS. The FBS does not distort the airway anatomy, and the patient breathes spontaneously during the examination. In rigid endoscopy, the airway is held open and, in many cases, ventilation is controlled by the anesthesiologist. Laryngomalacia, tracheomalacia, and pharyngeal collapse or narrowing are examples of lesions with important dynamic findings that are best evaluated by flexible bronchoscopy.

There are several types of problems that are best treated or evaluated using rigid bronchoscopy. In

cases of suspected epiglottitis, the rigid bronchoscope should be used to establish an airway and to maintain ventilation before placement of an endotracheal tube. The FBS does not allow the endoscopist to lift or displace the swollen epiglottis and cannot be used to ventilate small children. In cases of massive hemoptysis, the suction capabilities and the ability to provide ventilation make the rigid bronchoscope superior to the FBS. The ability to maintain ventilation and the range of forceps available make rigid bronchoscopy safer and more desirable for the removal of intrabronchial foreign bodies. Finally, the rigid bronchoscope is superior for airway surgery, such as the removal of granulation tissue from proximal airways. Again, the ability to control ventilation and the range of instrumentation available are advantages of the rigid approach.

In the only published comparison of flexible and rigid bronchoscopy in a series of adults,[35] complications were higher with rigid bronchoscopy than with flexible bronchoscopy.

Complications of bronchoscopy are unusual, but precise comparison of the two techniques is difficult for several reasons. First, published series of rigid bronchoscopies often do not include anesthetic complications,[36] whereas series of flexible bronchoscopies do include anesthesia-related problems.[11] Secondly, the rigid endoscopist must treat patients with massive hemoptysis or acute airway obstruction from epiglottitis or foreign body aspiration. These conditions make the rigid procedure more risky than most flexible bronchoscopies.

Whether to examine the airway by flexible or rigid bronchoscopy is a decision that depends upon the patient, his or her clinical problem, the equipment available, and the training and experience of the bronchoscopist. In some cases, one approach is clearly superior, whereas in other cases either approach may be acceptable. The chosen approach should maximize the benefits for the patient while minimizing the risks.

Clinical Applications of Flexible Bronchoscopy in Neonates

The indications and efficacy of flexible bronchoscopy in infants have been documented by several authors.[28,29,37,38] Cohn et al[38] have shown that flexible bronchoscopy is relatively safe even in infants with bronchopulmonary dysplasia.

The indications for flexible bronchoscopy in neonates are similar to the indications in children as listed in Table 2. Inspiratory stridor is caused by narrowing of extrathoracic airways. This may be due to laryngomalacia, vocal cord paralysis, subglottic stenosis, or a subglottic hemangioma. Monophonic expiratory wheezing is caused by narrowing of intrathoracic airways. Common causes include tracheomalacia, bronchomalacia, airway stenosis from granulation tissue, and airway compression due to cardiovascular structures. Polyphonic wheezing is often due to asthma. More comprehensive lists of causes for stridor and wheezing can be found in Tables 5 and 6. Persistent atelectasis may occur in cases of bronchomalacia or airway stenosis, but, most often, mucus plugging is present without other anatomic problems. In these cases, the mucus can be suctioned away, and prompt resolution of the atelectasis usually follows.

The diagnosis of persistent pulmonary infiltrates is aided by the technique of bronchoalveolar lavage. Neonates may only tolerate a few milliliters of lavage fluid, but this is adequate for multiple stains and cultures. In addition to stains and cultures for bacterial, fungal, and viral pathogens, stains for *Pneumocystis carinii* can be carried out.[39] The

Table 5. Causes of Stridor in Pediatric Patients

Craniofacial dysmorphology (Pierre Robin syndrome, Treacher-Collins syndrome)
Macroglossia (Wiedeman-Beckwith syndrome, Down syndrome)
Laryngomalacia
Congenital or acquired subglottic stenosis
Laryngeal webs
Vocal cord paralysis
Vascular rings and slings
Intrinsic and extrinsic tumors or cysts
Epiglottitis
Croup
Bacterial tracheitis
Foreign bodies in the airway or esophagus
Laryngeal papillomatosis
Postintubation edema

Table 6. Causes of Wheezing in Pediatric Patients

Asthma
Bronchiolitis
Vascular rings and slings
Anomalous innominate artery
Pulmonary hypertension
Congenital heart diseases
Foreign bodies in the airway or esophagus
Bronchial stenosis (congenital or acquired)
Tracheomalacia or bronchomalacia
Cystic fibrosis
Mediastinal cysts or tumors
Tuberculous lymph nodes

diagnosis of pulmonary hemorrhage can be made by examination for hemosiderin-laden macrophages.[40] Finally, lipid-laden macrophages have been used as a marker for aspiration of formula.[41]

Upper-airway obstruction, especially when caused by pharyngeal lesions, may present without snoring or stridor in some neonates. The site of obstruction in such patients can be readily determined by flexible endoscopy.

The FBS is a valuable aid to intubation in patients whose larynx cannot be visualized by standard rigid laryngoscopy. Examples of such patients include cases of severe micrognathia or patients with cystic hygroma of the pharynx. The technique has been described elsewhere.[42,43]

Summary

Flexible bronchoscopy has come into wide use in pediatrics during the past decade. It is a relatively safe technique that can often be performed on an outpatient basis. Flexible bronchoscopy is a valuable diagnostic tool and can be helpful therapeutically in selected cases. Flexible bronchoscopy and rigid bronchoscopy should be viewed as complementary rather than competing techniques. The next decade should bring further improvements in instrumentation and an even wider use of flexible bronchoscopy in infants and children.

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Discussion begins on next page.

Green Discussion

Stark: Chris (Green), I wonder if you could expand your comments a little more on the role of bronchoscopy in newborn infants who have lobar atelectasis or have difficulty being extubated for upper-airway reasons? I can't figure out whether we are underutilizing this procedure or just 'doing fine' by using it only occasionally.

Green: I think the two applications that you mentioned are two of the most useful for this technique in the neonatal intensive care unit. If the child with atelectasis is not in extremis, is treated with chest physiotherapy, and the atelectasis resolves with no further problems, there's no reason for bronchoscopy. But, for the infant who has persistent atelectasis that doesn't respond to medical therapy of some kind, flexible bronchoscopy can be very helpful. I have examined many children with atelectasis from a thick mucus plug. Using the flexible bronchoscope, you can direct the suction exactly to the plug and pull it out. If you use a blind technique with a suction catheter through an endotracheal tube, you can't direct the suction. Also, you have the Murphy hole on the side of the suction catheter, so you can't get full suction right on the plug. The plug has to be loose to be removed with a suction catheter. So, flexible bronchoscopy can be useful in the neonate with persistent atelectasis.

Next you mentioned the patient who can't be extubated. In our institution, the neonatologists will first attempt extubation a couple of times. If the child still can't be extubated, some anatomic lesion is probably present in the airway, and, I think the child ought to be examined. In some institutions, the otolaryngologist examines and in others the pediatric pulmonologist examines. Regardless, I think the child who can't be extubated and who may have an airway problem ought to have a careful examination of the airway.

Carlo: Do you use something else, like the x-ray, in cases of persistent atelectasis in which you suspect a plug? Or do you just do bronchoscopy in all cases of persistent atelectasis?

Green: I've been fooled by x-rays. I don't think I can tell with certainty whether a child has a mucus plug or not from the the chest radiograph. In our nursery (and I assume your policy is similar), the nurses are encouraged not to suction past the end of the endotracheal (ET) tube. When Bob Wood was in Cleveland, he encouraged limiting suctioning in this way to decrease mucosal damage and granulation tissue formation in the lower airways; the incidence of atelectasis fell after suctioning was limited. Now with suctioning only the length of the ET tube, I rarely get calls from the nursery. We don't have a lot of problems with persistent atelectasis. But, to answer your question, if persistent atelectasis occurs, I go ahead with bronchoscopy. I can't tell just from the chest film whether a mucus plug or some other problem has led to atelectasis.

Orenstein: As a follow-up to that, Chris do you think that there is any truth to the saying that air bronchograms in an almost-whited-out lobe or lung speak of a more widespread problem than one discrete mucus plug—whereas, if you see a total white-out, there's more likely to be a proximal mucus plug? In other words, the air bronchogram is a poor prognostic indicator.

Green: Well, if you see an air bronchogram, it's very clear that you probably don't have a proximal mucus plug. But, we've examined some patients with persistent atelectasis, in whom we did not see a proximal mucus plug or other anatomic problems that would predispose to atelectasis. Small-volume lavage returned some small peripheral plugs. The atelectasis subsequently resolved. Again, I don't think the chest radiograph tells you whether bronchoscopy will help or not. I don't advocate bronchoscopy for every child who has atelectasis. I do believe that appropriate medical therapy should be tried first.

Pierson: Just to follow up on Dave Orenstein's question—at least in adults, that issue of the air bronchogram comes largely from a study by Marini in 1979[1] in which from the standpoint of clinical outcome, adult patients with acute lobar atelectasis and a branching air bronchogram seldom improved no matter what you did—and going in with the bronchoscope made no difference at all. My own experience is the same, even in patients without air bronchograms, in whom I assume there is mucus plugging. This may be one area in which the adult atelectatic lobe is different from that of the neonate. In my experience, if I were blinded to the x-ray, I doubt that I would be able to tell which lobe had collapsed, and I have seldom seen that elusive 'mucus plug' even when it ought to have been there.

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Chatburn: A few years ago at Rainbow Babies & Childrens Hospital, we developed a technique that we called low-frequency oscillatory ventilation through the suction channel of a flexible bronchoscope.[1] We found that with this technique we could ventilate paralyzed rabbits indefinitely even when the bronchoscope totally occluded the ET tube. My question is, How often in your practice do you get into a situation where there is either total occlusion of the ET tube with the scope or some other situation that would cause

hypoventilation problems? And, what do you do in that situation?

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Green: In brief, I perform brief examinations. In the NICU, we have a 2.7-mm-diameter ultrathin flexible bronchoscope and have acquired in the last month or so a 2.2-mm flexible bronchoscope that has distal flexion, but neither of these units has suction capability. You can pass these instruments through small tracheostomy or endotracheal tubes and examine the lower airway. In the neonate, though, almost the whole tube is occluded by the bronchoscope. I make sure the child is well-oxygenated, pass quickly down the tube, and limit my examination to about 30 seconds. I have read the paper describing the technique that you developed. It is an interesting technique. As far as I'm aware, that technique has not been used outside of Cleveland. Because I am not doing surgery in the airway, I can usually perform the diagnostic exam I need in 30-45 seconds; therefore, I haven't pushed to develop alternative techniques. If you need to perform a prolonged procedure, then the technique you described could work very nicely.

Fanaroff: To give you some more historical perspective, Bob Wood was a tremendous zealot. In fact, when he got his first bronchoscope he used to arrive before the neonatologist. He was slowed down considerably when someone in central service boiled his flexible scope. He had to wait a long time until the next one came from Japan. I think the important lesson that we learned from the flexible scope—and I would like to emphasize this—is that suctioning is actually doing bad things to the baby rather than good things, particularly with catheters going well beyond the end of the ET tube. Bob clearly showed that what we were doing was biopsying the airway rather than clearing it. That changed practice—it sounds as if it has changed practice across the country—and I think that's a good thing! I think we should all question the way we suction babies. When we look at the inadvertent extubations in the unit, a high proportion of them relate to suctioning (personal experience, Rainbow Babies & Childrens Hospital, QA analysis). I'm not sure how much good we do with suctioning. You mentioned using the scope for diagnosis of anatomic problems. My impression has been that the MRI (magnetic resonance imaging) and the CT (computed tomography) scans are really spectacular in the newborn. Do you have a feel for what lesions you can better visualize with the bronchoscope than with these radiologic techniques?

Green: I don't really have any experience with MRI and the lungs in children, with the exception of one child who was extremely ill with cardiomyopathy, in whom we were able to demonstrate compression of the left-lower-lobe bronchus. We believed this child to be in such poor condition that she wouldn't have tolerated sedation for bronchoscopy. That's the limit of my experience.

CT has certainly been shown to be an excellent measure of bronchiectasis; therefore, bronchograms have almost disappeared in many parts of the country. If you are able to keep a child very still (and some of these units have gating for the respiratory cycle) you can get an idea of static findings in the airway. But, you can't get the kind of dynamic information from inspiration and expiration with CT, and I think not from MRI, that you can with flexible bronchoscopy. For instance, I think you have to be either very good or very lucky to demonstrate bronchomalacia or tracheomalacia on the CT, but it's easy to see with a flexible bronchoscope.

MRI with sedation runs close to $1,000. Flexible bronchoscopy is less expensive—about $700. Children at our institution have to be fairly heavily sedated for MRI, and these scans take a lot of time. We should consider the expertise in our institutions and decide for each patient what's best. You (Fanaroff) had another question before that—relating to suction?

Fanaroff: It was just a generic question on reexamining suctioning practice.

Carlo: You have to be careful when interpreting the results or data from upper-airway dynamics because, when you're obstructing the bronchus, you're likely to meet very high resistance. How do you evaluate that? The other thing is that you're also anesthetizing the upper airway—which might also cause dysfunction of the upper-airway muscles.

Green: I think, for exactly that reason, that the findings of bronchoscopy have to be interpreted in the clinical context of the patient. Take patients with no symptoms of upper-airway obstruction at all, give them enough sedation, and they exhibit upper-airway obstruction during bronchoscopy. I don't think sedation-induced findings are usually clinically relevant. I have to use my judgment, in the context of each patient, to decide how relevant such findings are. Similar problems occur with rigid bronchoscopy. The airway is held open with the rigid bronchoscope or laryngoscope, the child is under general anesthesia, sometimes spontaneously ventilating, and at other times ventilated by the anesthesiologist. These interventions also affect airway dynamics—so, there are always these judgments that come into play. Your point is a good one.

Dynamic airway movements can be exaggerated during flexible bronchoscopy. Proper interpretation requires experience and good judgment.

O'Rourke: I would just like to add a few words of caution. One relates to the issue of sedation. It behooves all of us to look very critically at those doing flexible bronchoscopy because some are delivering general anesthesia in a very uncontrolled environment and, in fact, losing protective airway reflexes. In the anxious child, there is a very small margin of error between safe sedation and uncontrolled oversedation. The second caution I would add is that, although flexible bronchoscopy is better for bronchoalveolar lavage (BAL) than rigid bronchoscopy, the window for safe flexible BAL is limited. Unfortunately, there are many times when we are asked to do flexible-bronchoscopy BAL in a child who is on 100%-oxygen via face mask and who has oxygen saturations in the 80% range. In these situations, the child should be taken to the operating room where BAL can be done through a protected airway (endotracheal tube or rigid bronchoscopy).

Green: In adult medicine, many flexible bronchoscopies with BAL are done much earlier in the lung disease. At our institution, we see some very ill children in whom we simply can't accomplish the lavage at the bedside in the ICU. The child is too sick, and it's not a safe procedure. For example, the child on 80-100% oxygen and a small endotracheal tube cannot be safely extubated for BAL.

In regard to your (O'Rourke) first comment on sedation, I'd like to elicit a further comment from you or anyone else in the group. I don't think there is an ideal pediatric sedative. I feel that I'm pretty successful at sedating these kids adequately and not getting into trouble with it. Sedation is certainly more difficult in the child who has had many other procedures and requires more sedation. You can get into a problem with hypoventilation in heavily sedated children. How do you deal with that in your institution?

O'Rourke: I think what has worked best have been the short-acting benzodiazepines. Getting away from narcotics as the primary drug has helped. A number of people still use barbiturates or ketamine—not knowing who is using them or how much they are using is worrisome. The concern with short-acting barbiturates such as Brevital (methohexital sodium) is that an inadvertent overdosage would result in hypoventilation or apnea plus loss of airway reflexes. That short answer to your questions is short-acting benzodiazepines.

Green: I agree with your comments! These drugs are potentially dangerous, so we have to use them carefully.

Principles and Practice of Neonatal and Pediatric Mechanical Ventilation

Robert L Chatburn RRT

Introduction

To safely and effectively provide mechanical ventilation for infants and children one must have (1) an understanding of the physiologic effects of mechanical ventilation in terms of both gas exchange and pulmonary mechanics; (2) a working knowledge of ventilator design and operation; (3) an appreciation of the particular disease processes leading to the need for mechanical ventilation, and (4) experience, because infant and pediatric ventilation is as much art as science. In this paper I first review some of the major physiologic effects of mechanical ventilation. Next, I describe the fundamentals of ventilatory mechanics that provide the essential framework for understanding the patient-ventilator system. This conceptual framework is necessary for understanding ventilator design and operation. It is a systems analysis approach that facilitates the comparison of mechanical ventilators and modes of ventilation.

Physiologic Effects of Mechanical Ventilation

There are many ways to describe the indications and contraindications for mechanical ventilation. Harris[1] has presented the good and bad effects of assisted ventilation in a particularly instructive form: a set of goals, each with a corresponding complication to avoid (Table 1). A complete description of the complications of mechanical ventilation are beyond the scope of this discussion. However, I would like to briefly review the goals of ventilation in terms of how ventilator variables are managed clinically.

Table 1. Goals and Complications of Assisted Ventilation in Infants and Children*

Goals To Achieve	Complications To Avoid
Improved alveolar ventilation and maintainence of normal P_{aCO_2}	Hyperventilation and poor perfusion of the brain Alveolar overdistention/air leaks
Reduced $\dot{V}/\dot{Q}$ mismatch and maintainence of normal P_{aO_2} or S_{aO_2}	Oxygen toxicity to lungs (eg, BPD) Retinopathy of prematurity (ie, RLF) Hypoxemia causing tissue damage
Reduced work of breathing and elimination of respiratory muscle fatigue	Suppressed ventilatory drive Increased upper airway resistance
Re-expanded atelectatic or collapsed lung segments	Hyperinflation or over-expansion of normal areas of the lungs Pulmonary hypoperfusion Reduced venous return/ cardiac output

*Adapted, with permission, from Reference 1.

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Abbreviations Used in this Paper

ARDS	— Adult respiratory distress syndrome
BSA	— Body surface area
C	— Compliance
f	— Breathing frequency
F_{IO_2}	— Fractional inspired oxygen concentration
FRC	— Functional residual capacity
I:E	— Inspiratory-to-expiratory-time ratio
P_{aCO_2}	— Arterial carbon dioxide tension
P_{ACO_2}	— Alveolar carbon dioxide tension
P_{alv}	— Alveolar pressure
P_{aO_2}	— Arterial oxygen tension
P_{aO_2}/P_{AO_2}	— Arterial-alveolar oxygen-tension ratio
P_{atm}	— Atmospheric pressure
$\bar{P}_{aw}$	— Mean airway pressure
P_{bs}	— Pressure on the body surface
PCIRV	— Pressure-controlled inverse-ratio ventilation
PEEP	— Postive end-expiratory pressure
PIE	— Pulmonary interstitial emphysema
PIP	— Peak inspiratory pressure
P_{IO_2}	— Inspired oxygen tension
P_L	— Lung pressure
P_{mus}	— Ventilatory muscle pressure
P_{ta}	— Transairway pressure
P_{tr}	— Transrespiratory pressure
P_{tt}	— Transthoracic pressure
P_{H_2O}	— Water vapor pressure
R	— Resistance
RDS	— Respiratory distress syndrome
t	— Time
t_e	— Expiratory time
t_i	— Inspiratory time
$\dot{V}$	— Flow
V_A	— Alveolar volume
$\dot{V}_A$	— Alveolar ventilation
$\dot{V}_{CO_2}$	— Carbon dioxide output
V_D	— Dead-space volume
V_D/V_T	— Dead-space-to-tidal-volume ratio
$\dot{V}_E$	— Expired minute ventilation
V_L	— Lung volume
V_T	— Tidal volume

Maintenance of Alveolar Ventilation

Mechanical ventilation is simply an attempt to normalize the patient's ventilation-perfusion ratio. To some extent, ventilator manipulations can optimize lung perfusion, but the main goal is to control alveolar minute ventilation. Indeed, respiratory failure is defined[2] in terms of arterial carbon dioxide tension (P_{aCO_2}), which is inversely related to alveolar ventilation ($\dot{V}_A$) by the equation:

$$P_{aCO_2} \propto \frac{\dot{V}_{CO_2}}{\dot{V}_A}. \quad [1]$$

where $\dot{V}_{CO_2}$ is carbon dioxide output. Alveolar ventilation, in turn, is defined (at least for normal ventilatory frequencies) as:

$$\dot{V}_A = (V_T - V_D)f, \quad [2]$$

where V_T is tidal volume, V_D is dead-space volume, and f is frequency. Thus, it is clear that P_{aCO_2} can be manipulated by controlling the V_T and f. This model can be used as the basis for estimating appropriate ventilator settings.

Dead-space volume is affected somewhat by the configuration of the patient circuit, but this is usually a secondary consideration. The physiologic dead-space-to-tidal-volume ratio (V_D/V_T) is normally about 0.3, but it is usually greater than 0.6 in mechanically ventilated patients[3] due, perhaps, to the effect of elevated airway pressure on anatomic dead space and the ventilation-perfusion ratio. The V_D/V_T may be estimated using the equation:

$$\frac{V_D}{V_T} = \left(\frac{a\dot{V}_E}{p\dot{V}_E}\right)\left(\frac{P_{aCO_2}}{40}\right)0.33, \quad [3]$$

where $a\dot{V}_E$ is actual exhaled minute ventilation and $p\dot{V}_E$ is the exhaled minute ventilation predicted by using estimated V_T and f from the Radford nomogram (Fig. 1).

Given an estimate of the V_D/V_T and a desired P_{aCO_2}, the required $\dot{V}_E$ can be estimated from the graph in Figure 2. Minute ventilation is expressed in terms of body surface area because pediatric patients have such a wide range of sizes. Body surface area (BSA) in square meters can be estimated from the equations:

For infants weighing 2.5-20.0 kg—

$$BSA = \frac{(3.6)(\text{weight}) + 9}{100}. \quad [4]$$

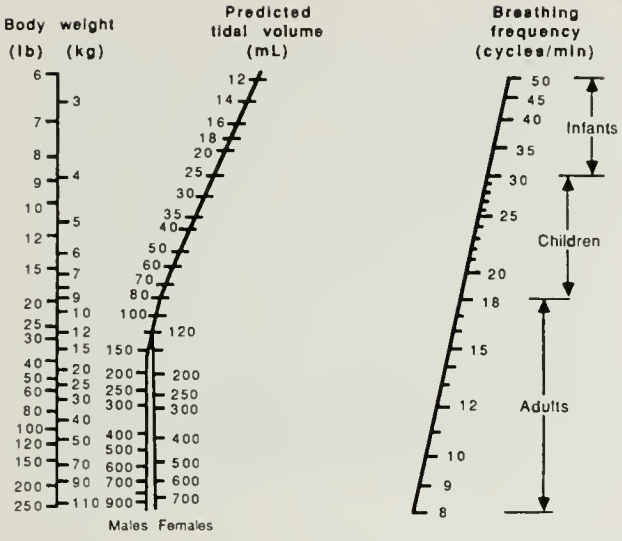

Fig. 1. The Radford nomogram to predict tidal volume based upon body weight and breathing frequency. Tidal volume should be corrected for fever: add 5% for each °F above 99 (rectal) or add 9% for each °C above 37 (rectal); and for high altitude: add 5% for each 2,000 feet above sea level or add 8% for each 1,000 meters above sea level; and for patients not in a coma: add 10%.

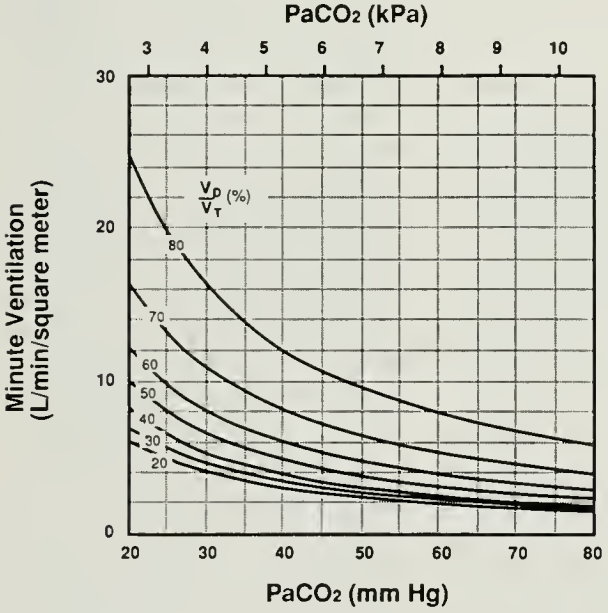

Fig. 2. Graph relating minute ventilation ($\dot{V}_E$) and arterial carbon dioxide tension (P_{aCO_2}) for different values of physiologic dead space (V_D/V_T) (assuming atmospheric pressure is 760 torr [101 kPa], body temperature is 37°C [310°K], and carbon dioxide output is 112 mL·min^{-1}·m^{-2}).

For children weighing 20.01-40.0 kg—

$$BSA = \frac{(2.5)(\text{weight}) + 33}{100}. \quad [4a]$$

Multiplying the estimated body surface area (BSA) by the $\dot{V}_E$ estimated from Figure 2 gives the $\dot{V}_E$ that must be delivered by the ventilator to achieve the desired P_{aCO_2}.[4]

It is interesting to note that the above mathematical models are based on the concept that the lungs are simply a flow-conducting tube (ie, the dead space) connected to a single elastic compartment (ie, the alveolar volume [V_A]). While such models provide a logical, although perhaps oversimplified, approach to ventilator management, I believe that clinicians seldom use them. Rather, they use a 'rule of thumb' such as 10 mL/kg for selecting an initial tidal volume,[3] and then arbitrarily select a frequency that, from experience, they believe will get them 'in the ballpark' for P_{aCO_2}. With practice, this approach seems to work quite well, and it is certainly quick. Subsequent adjustments of minute ventilation to alter P_{aCO_2} are also usually made arbitrarily on the basis of what experience suggests will work. There is, of course, a model based on the above relations that can also be used:

$$nP_{aCO_2} = \frac{(oP_{aCO_2})(of)(oV_A)}{(nf)(nV_A)}, \quad [5]$$

where n refers to new and o refers to old. This model may be simplified if the tidal volume is not changed:

$$nP_{aCO_2} = \frac{(oP_{aCO_2})(of)}{nf}. \quad [5a]$$

If a change in tidal volume is desired, alveolar volume can be estimated by using the equation:

$$V_A = V_T\left(1 - \frac{V_D}{V_T}\right), \quad [6]$$

in which the estimated V_D/V_T is expressed as a decimal rather than a percentage.

Maintenance of Oxygenation

The most straightforward control of oxygenation is achieved by adjusting the oxygen concentration of inspired gas. However, there is rarely as direct a

relationship between fractional inspired oxygen concentration (F_{IO_2}) and P_{aO_2} as there is between $\dot{V}_E$ and P_{aCO_2}. To understand the chain of events, we begin with the calculation for the partial pressure of inspired oxygen (P_{IO_2}):

$$P_{IO_2} = F_{IO_2}(P_{atm} - P_{H_2O}), \quad [7]$$

where P_{atm} is atmospheric pressure and P_{H_2O} is water vapor pressure. This calculation shows that some of the inspired oxygen is displaced by water vapor. As inspired gas travels to the alveolar region of the lungs, some of the oxygen is displaced by carbon dioxide. The partial pressure of oxygen in the alveolus (P_{AO_2}) is estimated by the equation:

$$P_{AO_2} \approx P_{IO_2} - \frac{P_{aCO_2}}{0.8}. \quad [8]$$

It is evident that oxygenation is affected by both the inspired oxygen concentration and the level of ventilation. Unfortunately, this relationship is complicated by any diffusion-block disorder of the alveolar-capillary membrane and by the lung's overall ventilation-perfusion ratio. The overall effect of an abnormal ventilation-perfusion ratio is to lower the P_{aO_2}.[5] The ventilation-perfusion ratio of the lungs is affected by the pattern of mechanical ventilation. Mean airway pressure ($\bar{P}_{aw}$) is a useful index of the overall effect of changes in ventilation variables such as peak and end-expiratory pressure and the ratio of inspiratory to expiratory time (I:E). In general, oxygenation increases as $\bar{P}_{aw}$ increases up to the point at which the lung becomes overdistended.

P_{aO_2} as a function of F_{IO_2} and ventilation may be estimated[6] by the nomogram illustrated in Figure 3. If an arterial to mixed-venous oxygen-content difference of 5 mL/100 mL is assumed, 'virtual shunt' may be estimated[7] from the graph shown in Figure 4.

Avoiding Barotrauma

Pulmonary barotrauma results in such disorders as pulmonary interstitial emphysema (PIE), pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema.[8] Clinicians typically think of high peak inspiratory pressure (PIP), or possibly positive end-expiratory pressure (PEEP), as being responsible for barotrauma.[8,9] Ac-

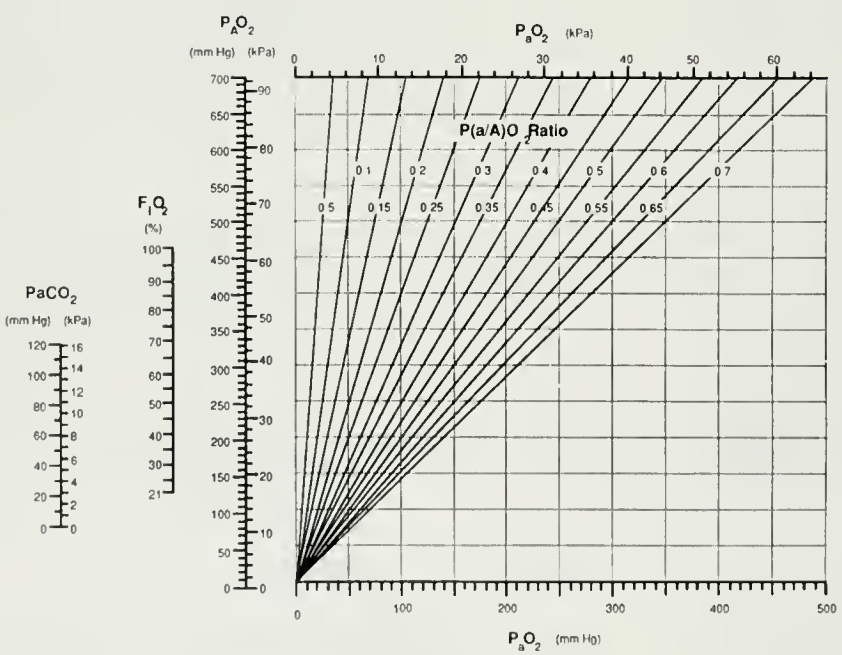

Fig. 3 Arterial-alveolar oxygen-tension-ratio (P_{aO_2}/P_{AO_2}) nomogram. If the old (ie, current) P_{aCO_2}, F_{IO_2}, and P_{aO_2} are known, the F_{IO_2} required for a desired P_{aO_2} can be estimated by assuming that P_{aO_2}/P_{AO_2} remains constant. A straight line connecting the old P_{aCO_2} and old F_{IO_2} will intersect the old P_{AO_2}. P_{aO_2}/P_{AO_2} is represented by the diagonal line connecting the origin of the graph (P_{AO_2}=0, P_{aO_2}=0) and the point representing the old P_{AO_2} and old P_{aO_2}. For example, a P_{aCO_2} of 40 torr [5.3 kPa] and an F_{IO_2} of 0.40 result in a P_{AO_2} of about 240 torr [31.9 kPa]. If the measured P_{aO_2} is 50 torr [6.7 kPa], P_{aO_2}/P_{AO_2} is about 0.2. If one moves along this diagonal line to a point above the desired P_{aO_2} (eg,80 torr [10.6 kPa]), a horizontal line to the left of this point intersects the P_{AO_2} line at 400 torr [53.2 kPa]. A line connecting this number to an expected P_{aCO_2} of 40 torr indicates that an F_{IO_2} of about 0.50 will be required.

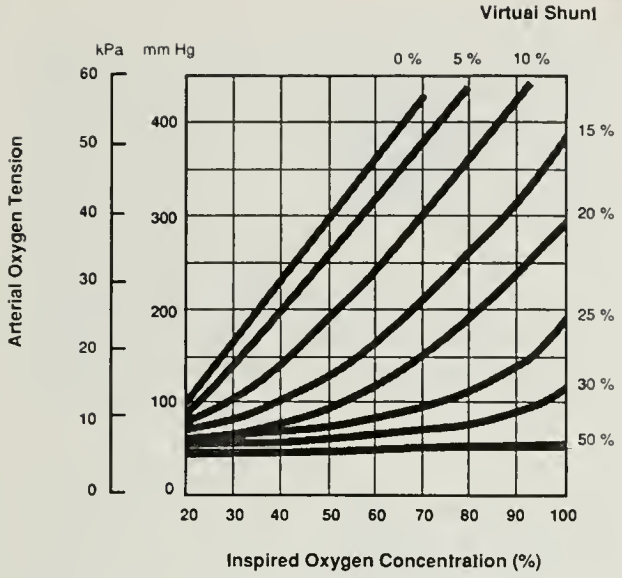

Fig. 4. Graph relating arterial oxygen tension and inspired oxygen concentration for different values of virtual shunt (assuming arteriovenous oxygen-content difference of 5 mL/dL). The shaded lines represent hemoglobin concentration range of 10-14 g/dL and P_{aCO_2} range of 25-40 torr [3.3-5.3 kPa].

tually, this is something of a misconception fostered by the literal meaning of the word barotrauma (ie, pressure injury). Thibeault and Lang[10] define barotrauma as "any *response* of the lung to pressure or force that results in pathologic changes in the lungs." The response of the lungs to an applied pressure is expansion. Thus, it is volumetric overexpansion and tearing of lung tissue that is responsible for barotrauma, not the application of pressure per se. A simple analogy makes this clear: Assume that a child's toy balloon will burst if inflated to a pressure greater than 100 cm H_2O. If this balloon is placed inside a metal container, it will not burst even if a pressure of several thousand centimeters of water is applied. Similarly, a balloon with thicker walls will require more than 100 cm H_2O to burst.

Excessive volumetric expansion is prevented in the first case by limiting the *transmural pressure difference* (ie, the walls of the metal container push against the outside of the balloon with the same pressure as that being exerted on the inside of the balloon). This assumption has been verified in several animal studies[11-13] by demonstrating that if the chest wall is bound, preventing overdistention of the alveoli, then even high airway pressures will not cause alveoli to rupture. On the other hand, high-volume ventilation using a negative-pressure iron-lung ventilator, with no applied airway pressure, does result in lung injury.[13,14]

In the second case, overexpansion is prevented by decreasing the compliance of the balloon (ie, increasing the elastic recoil force opposing the pressure inside the balloon). Therefore, it is too simplistic to think of airway pressure alone (or even transrespiratory system pressure) as being responsible for barotrauma. The combined effects of *transpulmonary pressure* and *compliance* must be considered as primary factors. It is not just a matter of high pressure or large tidal volume, but whether overdistention occurs at a given tidal volume and lung compliance.[14] In other words, a given tidal volume may be innocuous if delivered on the steep portion of the lung's volume-pressure curve, but may be detrimental if delivered on the flattened portion (eg, by elevating PEEP).

It has been observed that barotrauma occurs in two distinct patterns: PIE, and pneumomediastinum or pneumothorax. PIE is more common in preterm than in full-term infants.[15,16] Air leak in full-term infants is usually in the form of pneumomediastinum or pneumothorax.[10] The consequences are different as well. A pneumothorax is easily treated by drainage of pleural gas and rarely results in chronic lung damage, whereas diffuse PIE is difficult to treat and is often followed by chronic pulmonary insufficiency.[10] These clinical observations, supported by animal studies,[17-20] lead to the generalization that "the easily expandable lung is more prone to develop a pneumothorax without diffuse PIE, and the surfactant-deficient lung is more likely to develop diffuse PIE without a pneumothorax. This further implies that surfactant, not gestational age or maturity, is the critical factor in determining which of the two types of air leak will result."[10] Furthermore, in surfactant-deficient lungs, the *small airways* are the site of initial lung damage; whereas in lungs with surfactant, alveolar rupture is more likely to occur.[10] Because surfactant deficiency is a factor in adult respiratory distress syndrome (ARDS) as well as in infant RDS, it is reasonable to expect these two patterns of barotrauma to be evident in a wide range of pediatric patients from preterm infants to adolescents.

Normal Lung Morphology

To understand the etiology of pulmonary barotrauma, it is instructive to review the morphology of normal and surfactant-deficient lungs and their patterns of expansion during inspiration. Figure 5 illustrates the forces acting on the terminal airways and alveoli of a normal lung. There is an applied airway pressure of 12 cm H_2O [1.2 kPa]. Because the alveoli and small airways are lined with surfactant, their opening pressure is low, and the applied pressure equilibrates if given enough time. The airway pressure is transmitted to the terminal airways, alveolar duct walls, and alveoli. Pressure is transmitted among alveoli by collateral gas flow through the pores of Kohn, canals of Lambert, and interbronchiolar channels of Martin.[21,22]

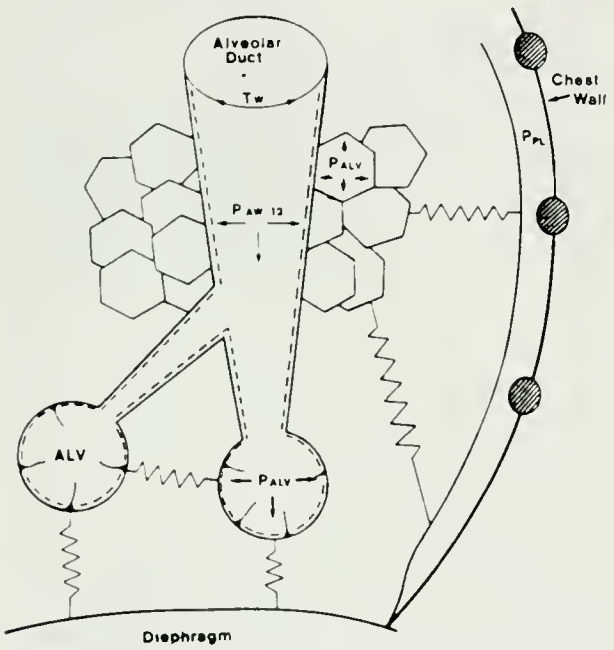

Fig. 5. Schematic diagram of a mature alveolar duct and alveoli. The dotted line represents surfactant. T_w is the wall tension that generates recoil pressure, P_{aw} is airway pressure (12 cm H_2O), P_{ALV} is alveolar pressure, P_{PL} is pleural pressure, and ALV is alveoli. (Adapted, with permission, from Reference 10.)

The terminal airways expand and lengthen as the alveoli expand, but not because of the airway pressure acting on their walls. The terminal airways are in physical contact with the alveoli (embedded in the elastic network of the alveolar septa), and thus the pressure difference across their walls is essentially zero. The traction on the airways is caused by the pressure difference between the alveoli and the pleural space, and varies with lung volume according to the pressure-volume characteristics of the lung. As alveoli expand and lung volume increases, traction on the airways by the septa increases and the airways dilate. This effect is known as mechanical interdependence. It is a stabilizing force because the change in traction opposes the change in airway size. Thus, for example, collapse of an airway results in stretching the surrounding parenchyma.[23]

It has been shown in mature animal lungs that air leak occurs in overdistended alveoli.[24] For air leak to occur, there must either be a large pressure gradient across the alveolar wall or extreme intercellular tension. Yet in the normal lung, alveolar pressures are equal so that, even with high applied pressure, intra-alveolar walls tend not to rupture. However, this does not hold true for areas in the lung where alveolar walls abut pleura, airways, connective tissue septa, or extra-alveolar blood vessels. Figure 6 illustrates the forces in these areas. As the alveoli expand during inflation, stress is generated in the peribronchial and perivascular sheaths. An opposing force is generated by the airway walls. The net result is a shear stress that, if great enough, can rupture the alveolar wall. Gas from ruptured alveoli moves preferentially into the low-pressure perivascular or peribronchial spaces, and dissects either back toward the hilum or out toward the pleura to eventually create a pneumomediastinum or pneumothorax.[10]

Surfactant Deficiency and Immaturity

The chain of events leading to air leak in surfactant-deficient lungs is somewhat different. The small, highly compliant bronchioles and transitional ducts in a surfactant-deficient, immature lung are the most likely sites of tissue damage and rupture during inflation.[10] The lack of surfactant leads to increased surface-tension forces. This results in atelectasis and the pooling of liquid in saccules and small airways. The presence of an air-liquid interface is the major cause of difficulty in reopening airways and alveoli.[23] In addition, col-

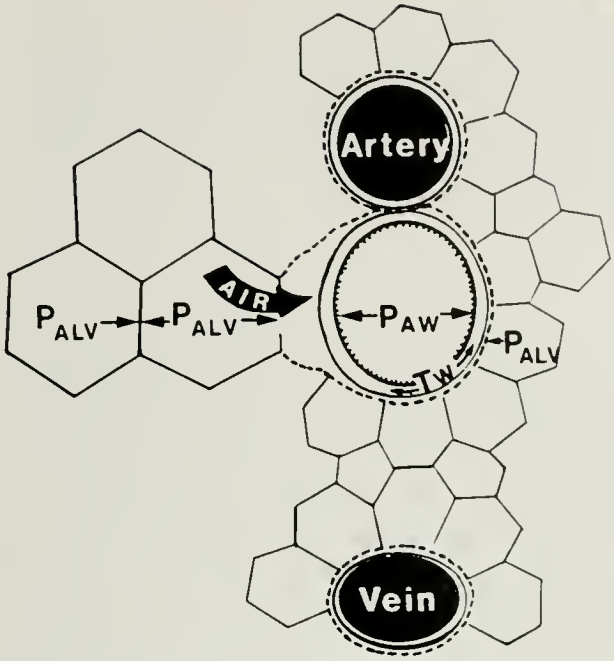

Fig. 6. Schematic diagram of the lung parenchyma showing artery, vein, small airway, and alveoli. The dotted lines represent separate connective tissue sheaths around the airway, artery, and vein. Airway pressure (P_{aw}) equals alveolar pressure (P_{alv}). Tw is wall tension. Overdistended alveoli (at left) have stretched the periairway sheath past its elastic limit and gas is shown escaping into the periairway interstitial space. (Adapted, with permission, from Reference 10.)

lapsed and liquid-filled saccules provide little outward tension on the small airways, and as a result the entire lung volume is low.

Figure 7 illustrates the effect of an applied airway pressure of 26 cm H_2O [2.5 kPa]. It has been shown[25] in immature rabbit lungs that the pressure required to overcome the surface-tension forces and to push back the liquid front is about 25 cm H_2O [2.5 kPa]. If the pressure is applied long enough, the liquid front may move outward and allow the alveoli to inflate. If this occurs, the terminal lung unit will look more like Figure 5. The terminal airways are at risk of becoming overdistended because they are very compliant (especially in immature lungs) and because the saccules and alveoli are collapsed and provide no counterbalancing force. In the immature lung, collateral flow is absent,[10] which tends to prevent expansion of collapsed areas. If a large transpulmonary pressure is applied to a nonuniformly expanding lung, the large stresses caused by lung interdependence could lead to hemorrhage and rupture.[26] Pressures as high as 60 cm H_2O [5.9 kPa] may be required to open some atelectatic areas.[27]

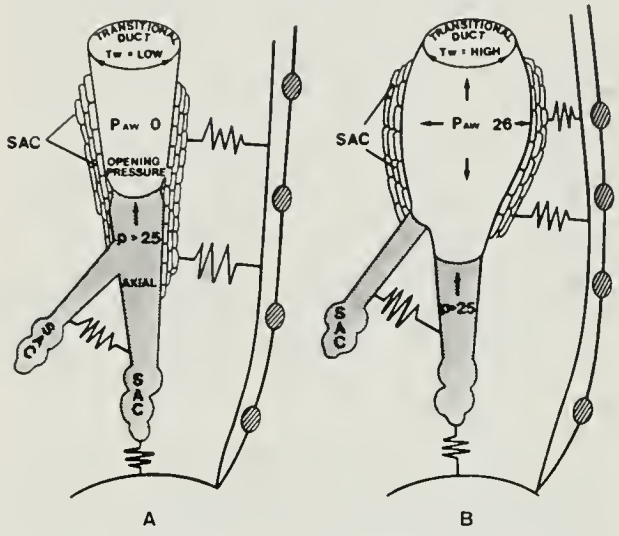

Fig. 7. A. An immature distal airway at end-expiration. The saccules (SAC) and airways contain liquid (shaded area), and the periairway saccules are collapsed. B. As inspiratory pressure rises, the distal airway is overextended and the liquid front is pushed backwards before the saccules inflate. T_w is wall tension, P_{aw} is airway pressure (in cm H_2O), and p is opening pressure (in cm H_2O) required to overcome surface-tension forces and to push back the liquid front. (Modified, with permission, from Reference 10.)

Mechanics of Ventilation

Like gas exchange, pulmonary mechanics are often based on a model of the lungs consisting of a single, cylindrical flow-conducting tube (representing the conducting airways) connected to a single, spherical elastic compartment (representing the alveoli) as shown in Figure 8. The normal lung is considered to be a homogeneous assembly of these units with pressure-volume and pressure-flow characteristics derived from the representative unit. Although such a model must be modified to explain observations (such as inhomogeneities of inflation, nonspherical alveoli, interaction of alveoli with the network structure of the parenchyma,[23] and the effects of the chest wall), it provides a good understanding of how the ventilator 'sees' the load imposed by the patient's respiratory system. Indeed,

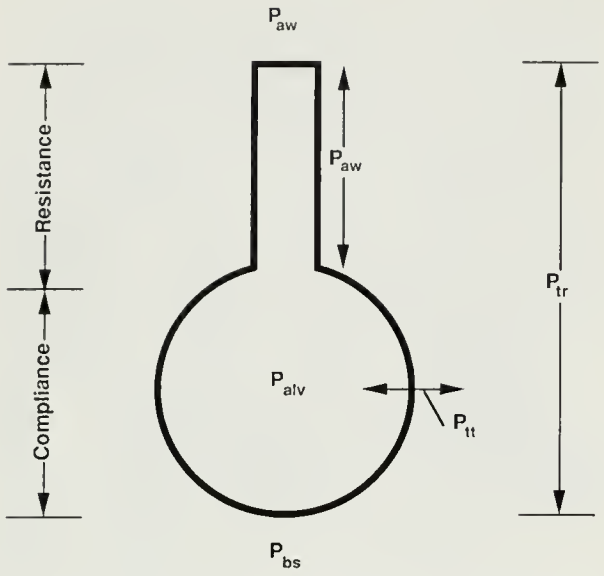

Fig. 8. A single-compartment model of the lungs consisting of a flow-resistive element connected in series with a compliant element. P_{aw} is airway pressure, P_{alv} is alveolar pressure, P_{bs} is body surface (ie, atmospheric) pressure, P_{ta} is transairway pressure ($P_{aw} - P_{alv}$), P_{tt} is transthoracic pressure ($P_{alv} - P_{bs}$) and P_{tr} is transrespiratory pressure ($P_{aw} - P_{bs}$). Note that when the ventilator manometer reads P_{aw}, it is gauge pressure (ie, relative to atmospheric pressure) and thus equivalent to P_{tr}.

the single-compartment model is universally used by ventilator manufacturers (and manufacturers of bedside pulmonary-function-measuring equipment) whose devices characterize the patient's lung mechanics in terms of compliance and resistance. This model is particularly useful for comparing the effects of pressure- and volume-controlled modes of ventilation.

Mathematical Models of Ventilatory Mechanics

The mathematical derivation of the single-compartment model of the lungs has been explained in detail elsewhere.[28] Briefly, the transrespiratory pressure (P_{tr}) required to cause inflation is conceived as having two components. One is the transthoracic pressure (P_{tt}) required to deliver a tidal volume against elastic recoil and the other is the transairway pressure (P_{ta}) required to overcome flow resistance:

$$P_{tr} = P_{tt} + P_{ta}, \qquad [9]$$

where P_{tr} = airway pressure – body surface pressure, P_{tt} = alveolar pressure – body surface pressure, and P_{ta} = airway pressure – alveolar pressure. The pressure required to cause inspiration may come from the ventilatory muscles (P_{mus}), the ventilator (P_{tr}), or both:

$$P_{mus} + P_{tr} = P_{tt} + P_{ta}. \qquad [10]$$

Transrespiratory pressure is the difference between airway pressure at the mouth (or endotracheal tube) and body surface pressure. Because ventilator manometers measure gauge pressure (ie, relative to atmospheric pressure), P_{tr} in Equation 10 is equivalent to the 'airway pressure' displayed by the ventilator. Thus, we can substitute P_{aw} for P_{tr} with the understanding that airway pressure is measured relative to body-surface pressure (ie, atmospheric pressure).

For a single-compartment model of pulmonary mechanics, the relations between pressure and volume and between pressure and flow are assumed to be linear. This means that the change in transrespiratory pressure is directly proportional to the corresponding change in lung volume. The constant of proportionality is the slope ($\Delta P/\Delta V$) of the pressure-volume curve (ie, elastance), although its reciprocal (ie, compliance) is more frequently used. Also, the change in transairway pressure is proportional to the change in flowrate and to the constant of proportionality ($\Delta P/\Delta \dot{V}$), ie, resistance. Substituting $\Delta P/\Delta V$ and $\Delta P/\Delta \dot{V}$ in Equation 10 yields an expression that is often called the *equation of motion* of the respiratory system:

For inspiration—

$$P_{mus} + P_{aw} = \frac{V}{C} + (\dot{V})(R), \qquad [11]$$

For passive expiration—

$$\frac{V}{C} = -(\dot{V})(R). \qquad [11a]$$

R and C are the resistance and compliance of the respiratory system; V is the volume inspired or expired, respectively; and $\dot{V}$ is inspiratory or expiratory flow, respectively. Note that during expiration, flow is driven by the pressure stored in the

elastic components of the lung ($P_{alv} = V/C$). Expiratory flow has a negative value signifying that it is in a direction opposite to inspiratory flow. Graphically, this is illustrated by drawing the inspiratory flow curve above the horizontal axis and the expiratory flow curve below the horizontal axis.

The equation of motion (Equations 11 and 11a) of the respiratory system has three main uses. First, if the ventilatory muscles are relaxed (ie, $P_{mus} = 0$), then we can take measurements of pressure, volume, and flow, at the bedside and calculate estimates of the patient's total respiratory system compliance and resistance. Second, given estimates of compliance and resistance, we can predict how much pressure will result from delivering a given tidal volume at a given inspiratory flowrate. Alternatively, we can predict how large a tidal volume and inspiratory flowrate will be delivered for a given pressure generated by the ventilator. Third, it forms the theoretical basis for a logical and consistent ventilator-classification system.

Figure 9 graphically illustrates the relations expressed in the equation of motion (Equations 11 and 11a). The set of graphs on the left in this figure shows ventilation with a constant inspiratory flowrate, while that on the right is with a constant inspiratory (transrespiratory) pressure, both of which are set to deliver the same tidal volume (20 mL) in the same inspiratory time (1 second). Note that the shape of the alveolar pressure curve is the same as that of the volume curve; only the units of measurement are different.

With a constant inspiratory flowrate, the initial rise in pressure seen on the ventilator manometer (4 cm H_2O in Figure 9) is equal to resistance × flow. The slope of the pressure rise is inversely proportional to compliance. The peak inspiratory pressure is due to compliance, tidal volume, resistance, and inspiratory flowrate as described by the equation of motion (Equations 11 and 11a). Lung pressure (P_L) and lung volume (V_L) may be described as:

$$P_L = \frac{(\dot{V})(t)}{C}, \qquad [12]$$

$$V_L = (\dot{V})(t), \qquad [13]$$

where P_L is lung pressure, t is time, and V_L is lung volume.

If inspiratory pressure is constant, then lung pressure, lung volume, and flowrate during *inspiration*

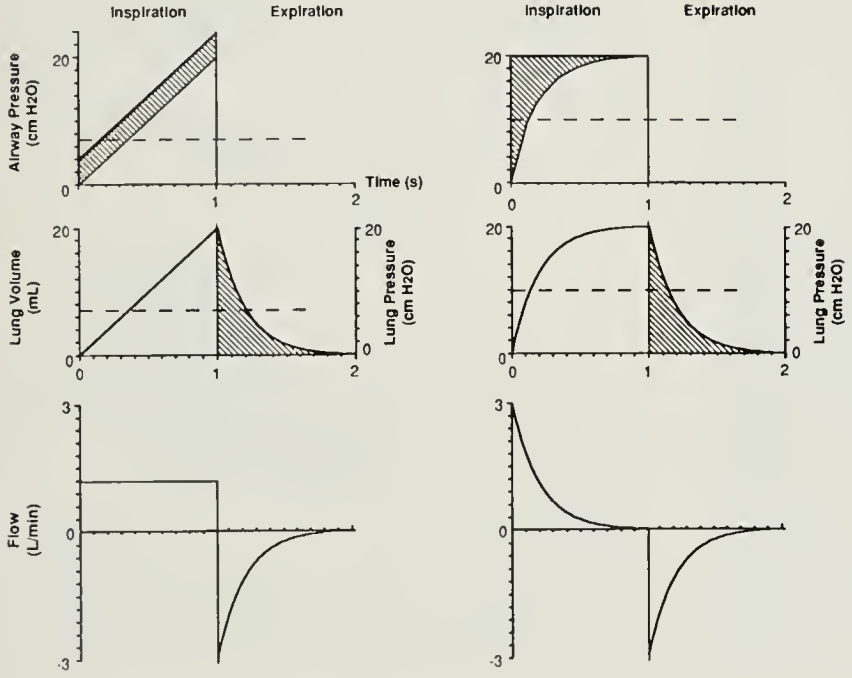

Fig. 9. Graphical representation of the equation of motion (Equations 11 and 11a) for a constant-inspiratory-flow pattern (left) and constant-inspiratory-pressure pattern (right). Pressure, volume, and flow are all measured relative to their baseline values at end expiration. The dotted lines indicate mean airway and lung pressures. The shaded sections represent equal geometric areas proportional to the pressure required to overcome flow resistance. The unshaded sections represent equal geometric areas proportional to the pressure required to overcome elastic recoil. Note that for the same tidal volume and mean inspiratory flowrate (ie, tidal volume ÷ inspiratory time), the constant-flow pattern produces a higher peak airway pressure and lower mean airway pressure than does the constant-pressure pattern, but the same peak lung pressure as does the constant-pressure pattern.

are exponential functions of time whose forms are derived from the equation of motion (Equations 11 and 11a):

$$P_L = \Delta P(1 - e^{-t/\tau}), \quad [14]$$

$$V_L = C(\Delta P)(1 - e^{-t/\tau}), \quad [15]$$

$$\dot{V} = \frac{\Delta P}{R}\left(e^{-t/\tau}\right), \quad [16]$$

where ΔP is the magnitude of the pressure change created by the ventilator relative to end-expiratory pressure (ie, peak inspiratory pressure – end expiratory pressure), t is inspiratory time measured from the start of inspiratory flow, e is the base of the natural logarithm (≈ 2.72), and τ is the *time constant* (R × C); resistance has units of (pressure × time)/volume and compliance has units of volume/pressure, so their product has units of time (usually seconds). As time passes, the volume of the lungs and alveolar pressure increases. As alveolar pressure approaches the peak pressure applied by the ventilator, inspiratory flow decreases. This is because the transairway pressure driving flow approaches zero (flow = $\Delta P/R$).

For any form of mechanical ventilation, *passive expiration* is described by:

$$P_L = \Delta P(e^{-t/\tau}), \quad [17]$$

$$V_L = C(\Delta P)(e^{-t/\tau}), \quad [18]$$

$$\dot{V} = -\frac{\Delta P}{R}\left(e^{-t/\tau}\right), \quad [19]$$

where t is expiratory time measured from the start of expiratory flow. Exponential equations may be somewhat difficult to appreciate intuitively at first, but the application of some basic mathematical principles reveals some interesting results. For simplicity, we will assume that both inspiratory and expiratory times are long enough to allow equilibration of airway and lung pressures. Keep in mind that all variables are measured relative to their value at end-expiration. This means that lung pressure is actually lung pressure above PEEP, and lung volume is volume above functional residual capacity (FRC). At end inspiration, lung pressure = ΔP + PEEP and lung volume = ΔV + FRC. The change in volume during inspiration (ΔV) is the tidal volume.

Inspection of the exponential equations for inspiration shows that when t = zero, $e^{-t/\tau} = 1$ so that lung pressure = zero, lung volume = zero, and inspiratory flowrate = $\Delta P/R$. When t = infinity, $e^{-t/\tau}$ = zero so that lung pressure = ΔP, $\Delta V = \Delta P \times$ compliance, and inspiratory flowrate = zero. A similar analysis can be applied to the expiratory equations.

For inspiratory or expiratory times between zero and infinity, the shapes of the lung-pressure, lung-volume, and flow curves are determined by the time constant. If these variables are plotted against time in units of time constants, a useful generalization is observed (Fig. 10). Regardless of the specific values of resistance and compliance, after a period of time equal to 1 constant, the variable achieves about 63% of its equilibrium value; after 2 time constants 86%; after 3 time constants 95%; after 4 time constants 98%; and after 5 time constants 99%. For practical purposes, equilibration is considered to be essentially complete after 5 time constants.

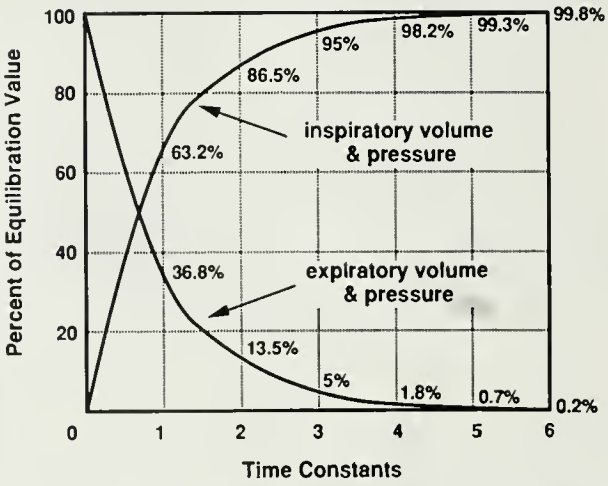

Fig. 10. The exponential rise and fall of lung pressure and lung volume during inspiration and expiration expressed in terms of time constants.

Figure 9 has more secrets to reveal. Both sets of pressure, volume, and flow curves were generated with a computer using the equation of motion (Equations 11 and 11a) and the same values of resistance and compliance (neonatal values in this case). Notice that the *peak airway pressure is*

greater for the constant-flow pattern than for the constant-pressure pattern, but the peak pressure in the lung is independent of the type of ventilatory pattern. Peak lung pressure depends only on compliance and tidal volume.

At each moment in time, airway pressure is equal to (volume/compliance) + (resistance × flow), in accordance with the equation of motion (Equations 11 and 11a). This could be appreciated geometrically if the scales for pressure, volume, and flow were adjusted (using compliance and resistance as scaling factors) such that the height of the flow curve plus the height of the volume curve equals the height of the airway pressure curve. Although the scales are not adjusted exactly this way, Figure 9 conveys this idea qualitatively.

The shaded portions of the pressure-time curves represent the pressure required to overcome flow resistance (ie, resistance × flow × time), whereas the white portions represent the pressure required to overcome elastic recoil (ie, volume × time/compliance). The shaded portions all have equal geometric areas. This result follows from the fact that the average inspiratory flowrate (ie, tidal volume/inspiratory time) in both cases is the same because the tidal volumes and inspiratory times are the same.

Although peak airway pressure is greater for the constant-flow pattern, mean airway pressure is less. $\bar{P}_{aw}$ is calculated as the area under the pressure-time curve divided by the time for one ventilatory cycle (Fig. 11):

$$\bar{P}_{AW} = \frac{\text{area}}{T_I + T_E} = K(PIP - PEEP)\left(\frac{T_I}{T_I + T_E}\right) + PEEP$$

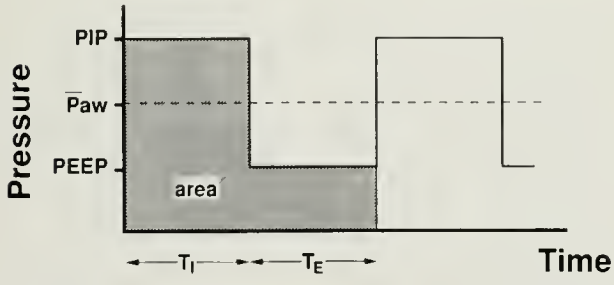

Fig. 11. Graph illustrating the definition of mean airway pressure ($\bar{P}_{aw}$). PIP is peak inspiratory pressure, PEEP is positive end-expiratory pressure, t_i is inspiratory time, t_e is expiratory time, and K is the waveform constant.

$$\bar{P}_{aw} = K(\Delta P)\left(\frac{t_i}{t_i + t_e}\right) + PEEP, \qquad [20]$$

where K is the waveform constant, PIP is peak inspiratory pressure, ΔP is the difference between PIP and PEEP, t_i is inspiratory time, and t_e is expiratory time. (K depends on shape of waveform and ranges from 1 for a rectangular wave to 0.5 for a triangular wave.) Note that $\bar{P}_{aw}$ is independent of ventilatory frequency if the I:E stays constant (assuming that K stays constant). In Figure 9, the $\bar{P}_{aw}$ on the left is 7 cm H_2O and on the right it is 10 cm H_2O. What about mean lung pressure? Because all shaded areas are equal (as discussed above), it should be clear from Figure 9 that the total area (for inspiration and expiration) under the airway pressure curve is equal to the total area under the lung pressure curve for each ventilatory pattern. The ventilatory cycle times are of course equal so that *mean airway pressure is the same as mean lung pressure.* This theoretical result has been substantiated in animals.[29] However, mean airway pressure may overestimate mean alveolar pressure if there is a substantial leak around the endotracheal tube.[30]

In 1973, Herman and Reynolds discovered that $P_{(A-a)O_2}$ decreased as $\bar{P}_{aw}$ increased in infants ventilated for RDS.[31] Since that time, many studies[32-37] have shown that $\bar{P}_{aw}$ is a useful index of the effect of the ventilatory pattern on oxygenation in both infants and adults. $\bar{P}_{aw}$ takes into account the important variables of the airway-pressure waveform including its shape, PIP, baseline pressure (PEEP), and the I:E; but $\bar{P}_{aw}$ more closely correlates with oxygenation than with any one of these other variables. Stewart et al[37] observed an average $\Delta P_{aO_2}/\Delta \bar{P}_{aw}$ of 4.9 in ventilated neonates. If $\bar{P}_{aw}$ was changed by changing PEEP, the ratio was 6.1; following PIP changes, the ratio was 5.1; and following I:E changes, the ratio was 1.9. Ciszek et al[35] have shown that if $\bar{P}_{aw}$ is held constant, changes in PEEP and I:E have no significant effect on oxygenation. They have also suggested[35] a direct relationship exists between the $\bar{P}_{aw}$ needed to oxygenate infants with RDS and the severity of the lung pathology—such that when $\bar{P}_{aw}$ is greater than 12 cm H_2O [1.2 kPa], complications may be anticipated.

Model Limitations

All of the above conclusions are valid only to the extent that the single-compartment model fits the actual behavior of the lungs. For practical purposes,[38] it probably does fit, but we should never lose sight of the fact that the model is a gross oversimplification. For example, the model assumes equal values for inspiratory and expiratory resistance, but in reality expiratory resistance tends to be greater than inspiratory resistance[39]—perhaps even 4.5 times greater.[40] This can cause mean lung pressure to be higher than mean airway pressure and can increase the risk of gas trapping. Also, we have assumed complete equilibration at end-inspiration and end-expiration. High ventilatory frequencies and/or long time constants tend to violate this assumption. Short inspiratory and expiratory times may lead to decreased tidal volume delivery and increased gas trapping (Fig. 12). The limitations of ventilation with a constant inspiratory pressure have been reviewed in detail by Marini et al.[41]

In the discussion of lung morphology related to barotrauma, it was noted that if surfactant is deficient, lung units tend to collapse on expiration, and then on inspiration small airways open before alveoli. This implies a two-compartment model with one compartment (the compliant terminal airway) connected in series with the alveolus or perhaps one collapsible lung unit in parallel with a normal unit (Fig. 13). If we postulate a lung unit in which collapse occurs on expiration and in which the alveolar opening pressure is 16 cm H_2O [1.6 kPa], then the possible effects on the two ventilatory patterns (constant-flow and constant-pressure) are illustrated in Figure 14. For both patterns, pressure rises in the terminal airway but not in the alveolus until the opening pressure is reached. At this point, pressure in the terminal airway drops slightly as gas escapes into the alveolus. The rates of pressure rise in the terminal airway and alveolus depend on the respective time constants. The major difference between the two ventilatory patterns is that the opening pressure is reached more quickly with a constant inspiratory pressure pattern. The result is that more time is available for the alveolus to fill, and hence alveolar

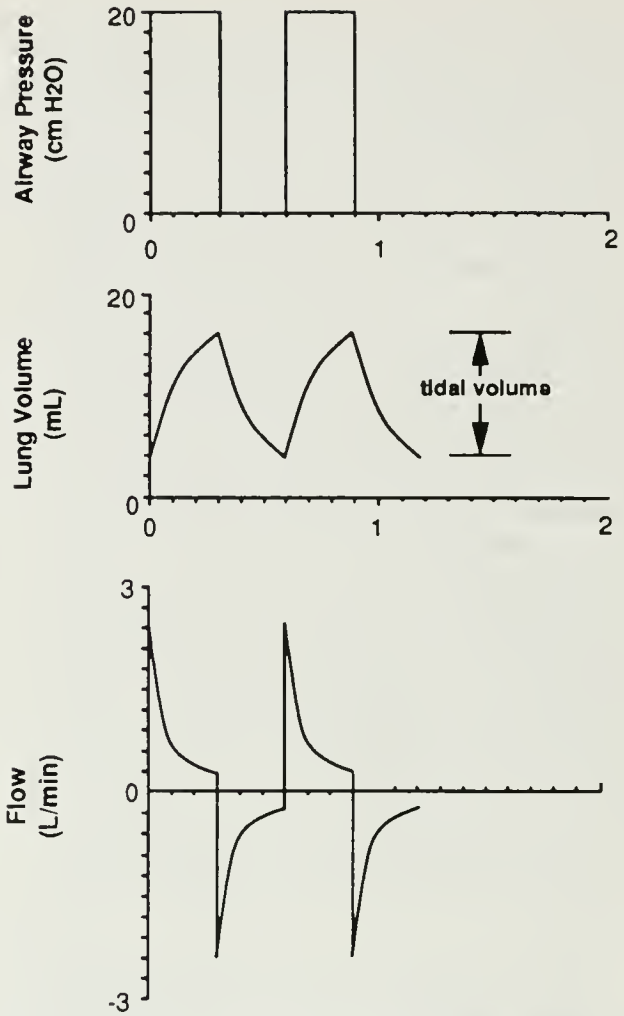

Fig. 12. Pressure, volume, and flow curves illustrating the phenomenon of alveolar gas trapping. Note that both inspiratory and expiratory times are so short that flow does not decay to zero. As a result, the tidal volume is less than it would be if complete inspiration and expiration were permitted.

ventilation and perhaps oxygenation is greater. One way to interpret this is that the constant-flow pattern results in greater dead-space ventilation than does the constant-pressure pattern, even though the exhaled tidal volume may be the same for both patterns. Thus, to achieve the same gas exchange, it may be necessary to increase the tidal volume using the constant-flow pattern with the consequence of distending the terminal airways even more and increasing the risk of barotrauma. The same type of argument can be applied to a lung model consisting of parallel compliances with different opening pres-

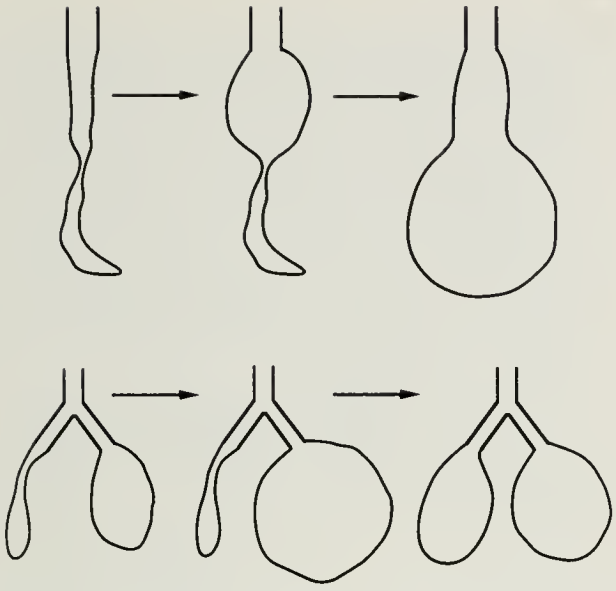

Fig. 13. Two ways of representing the lungs or lung units as double rather than single-compartment models. In both cases, the more compliant compartment overexpands before the collapsed compartment expands. Once the collapsed compartment opens, the tidal volume may redistribute more evenly between the two compartments.

sures and different time constants. In this case, a continuous inspiratory flowrate might overextend the lung units that are patent or have low opening pressure and normal compliance. Although these are unproven hypotheses,[42] they are consistent with some clinical observations.[43,44] A modification of the constant-inspiratory-flow pattern is to use an inspiratory hold. To my knowledge, this method—matched for tidal volume and $\bar{P}_{aw}$—has not been compared with the constant-inspiratory-pressure pattern, although the study by Lachmann et al[45] shows that inspiratory hold improves oxygenation.

Design Principles of Mechanical Ventilators

The difference in technical understanding between clinicians and those who design medical instrumentation grows larger with the introduction of each new device. Nowhere is this more evident than in the area of mechanical ventilation.

The extent of one's technical understanding is limited by the terminology used to describe different aspects of the technology. Published literature on the theory and application of mechanical ventilators is almost universally devoid of clear definitions and logical, consistent terminology based on a coherent theoretical framework. These failings are evident in the way clinicians talk about ventilators. Terms such as cycled, triggered, and limited are used interchangeably and as the basis for classifying differ-

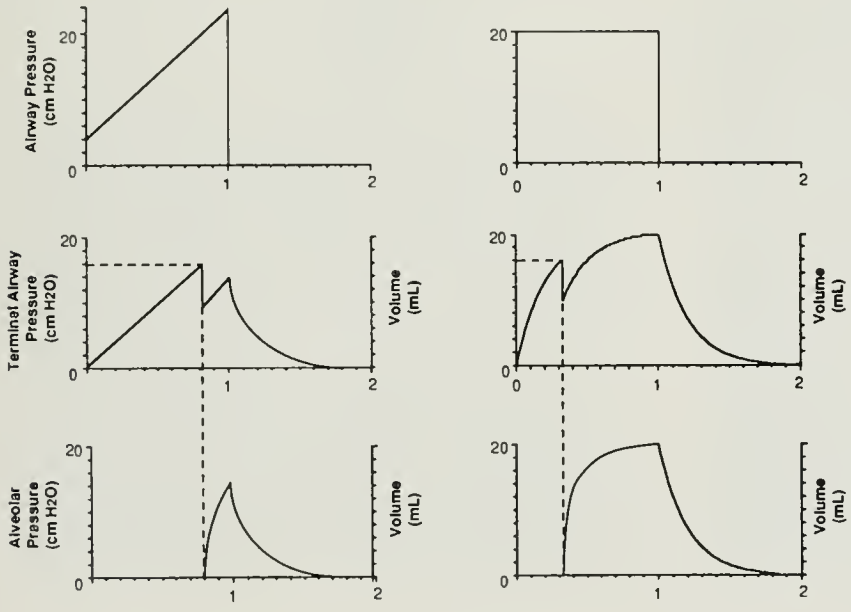

Fig. 14. Hypothetical pressure, volume, and flow curves for a two-compartment model consisting of a compliant terminal airway and a collapsed alveolus. The curves on the left are during constant-flow ventilation, and the curves on the right are during constant-pressure ventilation. Pressure and volume accumulate in the terminal airway until the opening pressure (16 cm H_2O [1.6 kPa]) of the alveolus is reached. At this point, pressure and volume fall momentarily in the terminal airway as the alveolus fills. Note that the constant-flow pattern leaves less time for the alveolus to fill than does the constant-pressure pattern, resulting in a smaller alveolar volume, a lower level of ventilation, and perhaps poorer oxygenation.

ent types of machines. Ventilation and ventilators are described as being volume- or pressure-controlled, volume- or pressure-preset, and constant volume or constant pressure. Different ventilator manufacturers use different words to mean the same thing in their operator's manuals. Perhaps the epitome of confusion comes in the form of new modes of ventilation such as pressure support, minimum minute ventilation, pressure-controlled inverse-ratio ventilation, and airway-pressure-release ventilation complete with acronyms. We are often reduced to 'hand-waving' in an attempt to get someone to understand what we mean rather than what we say. Even common modes of ventilation such as assist-control can apparently cause confusion: Some authors[46] have described patients in their study as "assisting their ventilators"! I am also continually amazed at the new ways that I:E may be adjusted. Therapists in my department tell me that they "rolled out," "pulled in," "extended," "tightened," "laid out," "brought in," "widened," "shortened," or otherwise manhandled the I:E. I'm not always sure what they mean when they say these things, but when I question them they can usually tell me whether the ratio has been increased or decreased.

Ventilator Classification

I believe that the key to understanding ventilators and modes of ventilation is the use of a logical and consistent classification scheme based on explicitly defined criteria. My colleagues and I have described in detail elsewhere[47] one such system. The major ideas of this system are presented in Figure 15. This system is based on the equation of motion (Equations 11 and 11a) as a model of the ventilator-patient interaction. From a basic understanding of this model, it follows that any conceivable ventilator can control one of three variables during inspiration: pressure, volume, or flow (time being an implicit variable)—hence, they are referred to in this context as *control variables*. Because volume and flow are inverse functions (ie, volume is the integral of flow, and flow is the derivative of volume), controlling one directly controls the other indirectly. As it turns out, it is most practical to control pressure and flow (rather than volume) as demonstrated by just about every new acute-care ventilator on the market (the Emerson models being a noted exception by virtue of their use of pistons). Most clinicians are familiar with the terms pressure ventilator and volume ventilator. I use the latter term to refer to machines that control inspired volume either directly (with a bellows or piston) or indirectly (by controlling the inspiratory-flow waveform).

For each control variable, manufacturers have settled upon only a handful of possible waveforms. The most common are rectangular (for pressure

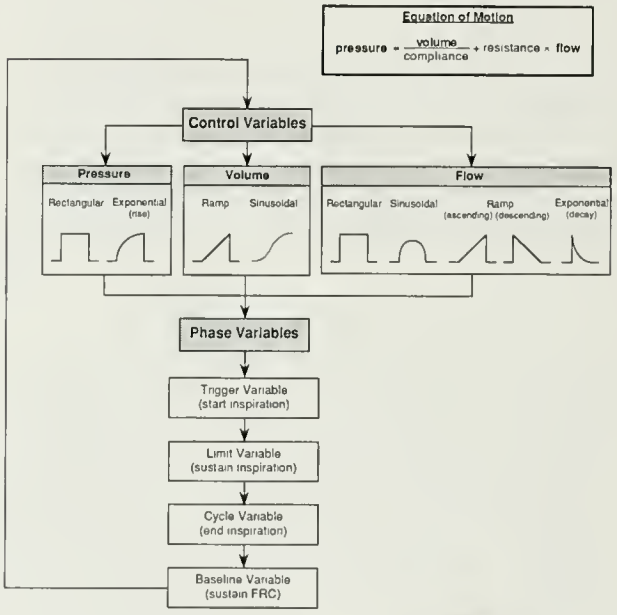

Fig. 15. Schematic diagram of a generalized ventilator-control scheme based on a single-compartment model of the respiratory system. During inspiration, the ventilator is able to control one and only one variable (ie, pressure, volume, or flow). Once this variable is selected by the operator, it is controlled to conform to a particular waveform (some common waveforms are illustrated). Pressure, volume, and flow can also be referred to as phase variables that constitute the clinically important parameters of each ventilatory cycle (eg, trigger sensitivity, peak inspiratory flow or pressure, inspiratory time, and PEEP). 'Modes' of ventilation are simply names for various combinations of control and phase variables. The diagram is drawn as a flow chart to emphasize that each breath may have a different set of control and phase variables depending on the mode of ventilation selected.

and flow control), sinusoidal (for volume and flow control), and ascending and descending ramp (for flow control). When volume and/or flow are used as control variables, the tidal volume may be preset and is simply a function of time and the preset inspiratory-flow pattern. When pressure is the control variable (eg, as in infant ventilation or during pressure support ventilation), the tidal volume is a function of time, compliance, resistance, and the amplitude of the pressure waveform (ie, the difference between peak and end-expiratory pressure).

Implicit in the equation of motion (Equations 11 and 11a) is that pressure, volume, and flow are functions of time and the ventilator must control the time intervals for inspiration and expiration. Years ago, Mushin et al[48] introduced the concept of dividing the ventilatory cycle into four phases: the change over from the expiratory phase to the inspiratory phase, the inspiratory phase, the change over from the inspiratory phase to the expiratory phase, and the expiratory phase. Ventilators are designed to monitor one or more of the control variables such that when the variables reach some preset values, a switch is made from one phase to another. Viewed in this context, pressure, volume, flow, and time can be referred to as *phase variables*. Specifically, four phase-variable categories can be defined: the *trigger* variable, the *limit* variable, the *cycle* variable, and the *baseline* variable. Modern ventilators combine control variables and phase variables within and between breaths.

In light of this classification scheme, some common misconceptions can be dispelled. First of all, for practical purposes, there are only three main types of ventilators: pressure controllers, volume controllers, and flow controllers. Theoretically, one can define a time controller (one that controls inspiratory and expiratory time),[47] but this type of ventilator is generally not used outside experimental environments.

It is very important to distinguish between the terms limit and cycle. A variable is limited if it reaches a constant value before inspiration ends. Inspiration is cycled off when a phase variable reaches some threshold value. For example, when ventilating infants, pressure is often the control variable and is limited to some peak value during inspiration (eg, the ventilator delivers a rectangular pressure waveform), but inspiration is terminated when the inspiratory time meets the value set by the clinician. Ventilators for older children and adults usually deliver a rectangular inspiratory-flow waveform (ie, inspiratory flow is limited at the operator-preset value), but inspiration is cycled off when the inspiratory time has reached the duration necessary to deliver the preset tidal volume (ie, tidal volume in this case is the product of time and flow). In other words, the clinician thinks he has set the peak inspiratory flowrate and the tidal volume using these knobs on the ventilator but, in reality, he has set inspiratory-flow limit and inspiratory time. Manufacturers, in effect, disguise the inspiratory-time knob by labeling it tidal volume in the interest of simplicity. Conversely, they may disguise the flow-limit control by labeling it minute volume whereas the inspiratory time is a function of the rate and percent-inspiration settings. The labels used depend on the particular philosophy of the manufacturer and on the market in which the ventilator is being sold (eg, Europeans seem to prefer to think in terms of minute volume while Americans prefer to think in terms of tidal volume).

A ventilator may use any or all of the possible phase variables for triggering, limiting, cycling, and controlling baseline. Indeed, the various 'modes' of ventilation (eg, assist-control, SIMV, pressure support) are simply shorthand notations for specific patterns of control variables and phase variables. For example, when the Siemens Servo 900C is in the assist-control mode with a rectangular flow pattern, it is a flow controller that is pressure- or time-triggered (depending on the sensitivity setting and the magnitude of the patient's inspiratory effort), flow-limited, time-cycled (or pressure-cycled if the airway pressure exceeds the alarm settings), and baseline-pressure (PEEP) controlled. The pressure-support mode, available on many new ventilators, is simply pressure-controlled ventilation that is pressure-triggered (again depending on the patient and the sensitivity setting), pressure-limited, and flow-cycled (ie, inspiration typically ends when the inspiratory flowrate decays to about 25% of its peak value).

Humidification

An important but often overlooked aspect of mechanical ventilation is the problem of humidification of inspired gas. There are actually two main problems, one having to do with physiology and one with methodology (ie, design principles and clinical application). First is the question of how inspired gas should be conditioned to mimic normal physiology when the upper airway is bypassed through use of an endotracheal tube. A recent review of the literature[47] suggests that gas delivered to the trachea should be heated to 32-34°C [305-307°K] and humidified to a water vapor content of 36-40 mg/L. But there are other physiologic concerns such as the maintenance of body temperature in premature neonates and the relationship between humidification and clinical outcome. These issues have just begun to be addressed in the pediatric literature.[50]

A consideration of the design principles of modern humidifiers and the complex clinical environments in which they are used reveals some interesting problems.[50] Heated humidifiers designed for use in intubated patients are intended to supply gas saturated with water vapor over a wide range of temperatures. The temperature and relative humidity of the gas leaving the device are affected by many factors including the surface area of the liquid-gas interface inside the humidifier, the gas flowrate and pattern, and the performance characteristics of the temperature controller. These factors are accounted for and controlled—to a large extent—by the particular device design. However, the temperature and relative humidity of the gas at the airway opening are largely affected by uncontrollable factors. Chief among these factors are the temperature and flow patterns of the air surrounding the patient circuit and the amount of incident thermal radiation (eg, from radiant warmers). Ambient air temperature can be above or below the desired temperature of inspired gas and can thus degrade the performance of the humidification system by the transfer of thermal energy across the walls of the patient circuit. Heating wires placed within the circuit to replace heat lost to room air can be effective in preventing pooled condensation, but they can cause other problems. Figure 16 illustrates one extreme situation that occurs when a patient circuit with heated wires passes through two distinct environments, room air at 29°C [302°K] and incubator air at 36°C [309°K].

The purpose of mentioning these issues is to call attention to the fact that humidification of inspired gas—particularly during neonatal ventilation—is more complicated than it appears. Furthermore, there is some experimental evidence[51] that links improper conditioning of inspired gas to an increased incidence of pneumothorax and severity of chronic lung disease in low-birthweight infants. Just as there is no ideal ventilator, so too there is no ideal humidification system nor is there any real consensus about how to use ventilators or humidification systems.

Controversies in the Application of Mechanical Ventilation

There is no generally-accepted 'right' way to ventilate infants and children, either by disease category or by type of ventilator. Even indications for ventilation and initial ventilator settings to use are subject to debate. However, there are several published references that cover these topics quite well.[52-57] Because this information is available, I will address some of the more philosophical issues of debate that are seldom explained in detail.

Volume Control versus Pressure Control

Mechanical ventilators have evolved along two distinct lines, those designed for adults and those for infants. I think the reason for this dual evolution lies in the inherent problems encountered in designing ventilators. It seems that the implicit assumption among those that make conventional ventilators is that the devices should be able to simulate the ventilatory muscles' ability to provide a consistent tidal volume in response to the patient's physiologic demand to breathe. However, two design problems immediately arise. First is the problem of how to generate the transrespiratory pressure necessary to deliver the required inspiratory volume and flow. Second is how to detect the patient's respiratory demand.

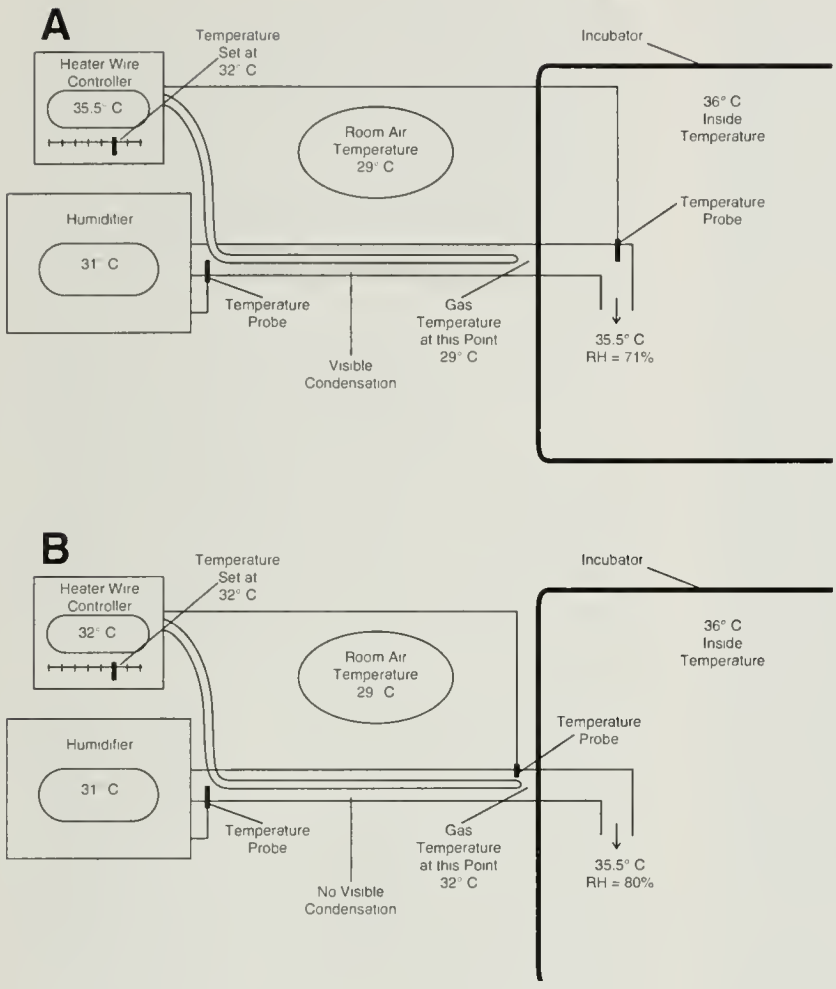

Fig. 16. Illustration of a problem encountered during the use of a patient circuit with a heated wire inside an incubator. A. When the temperature probe is placed inside an incubator whose temperature is set higher than the output temperature of the humidifier, the temperature of the inspired gas increases, the temperature probe sends a signal to shut off the heating wires, condensation forms in the circuit, and the relative humidity (RH) of inspired gas drops. B. When the probe is placed just outside the incubator, the heating wires function properly and the RH of the inspired gas is increased.

Under normal circumstances, the ventilatory muscles produce a nearly sinusoidal transpulmonary pressure, which in turn drives inspiratory volume and flow in a sinusoidal fashion. The earliest commercial ventilators, the so-called iron lungs, were successful, although primitive quasi-sinusoidal pressure controllers. But from an engineering standpoint, to design a more practical sinusoidal pressure controller one would need sophisticated pressure transducers, flow regulators, and feedback-control circuits. Such hardware has only recently become available. Even with microprocessor-controlled circuits, such a device still lacks the sophistication of the human body in its ability to adjust the pressure generated to maintain a consistent tidal volume via the Hering-Breuer reflex. It might be reasoned that the next best thing is a sinusoidal volume controller. Indeed, some of the earliest ventilators to replace the iron lung were of this design (eg, the Emerson and Engstrom ventilators). These devices relied on a rotating crank and piston to generate the desired waveforms. As technology progressed, it seems that the desire for sinusoidal waveforms was replaced by the desire for smaller, lighter, and more flexible devices. Hardware and electronics became available to control the flow of gas precisely and to generate a variety of inspiratory flow waveforms. Thus, we find ourselves in an era where almost every commercial ventilator made for adults is primarily a flow controller.

The second design problem, that of detecting the patient's ventilatory demand, has historically received less attention. Many of the first ventilators

ignored this problem altogether and simply delivered a preset number of mandatory breaths per minute. Around 1955, the first pressure-triggered ventilator was developed for anesthesia.[58] For about the next 30 years, pressure was the favored trigger variable. Until the late 1960s and early 1970s, mechanical ventilation was mainly reserved for adults. Then work by Reynolds and others[59,60] showed that mechanical ventilation could be applied to infants with respiratory distress syndrome.

Reynolds' early attempts at ventilating infants with a Bennett PR-2 resulted in adequate ventilation (ie, removal of CO_2) but poor oxygenation. The major problem was a lack of sensitivity of the pressure-triggering mechanism, which caused the infant to struggle against the ventilator. Efforts to set the ventilator rate at 60-80 breaths/min to synchronize with the infant's breathing pattern were not successful unless high peak inspiratory pressures (35-50 cm H_2O [3.4-4.9 kPa]) were used. Most patients died of bronchopulmonary dysplasia. Further experimentation[61,62] showed that if the PR-2 was modified to generate a rectangular pressure waveform at frequencies of about 30 breaths/min, two things happened: Peak airway pressures were reduced, and oxygen tension was improved. Subsequently, I-E ratios greater than 1:1 were recommended to further improve oxygenation.[63,64] These developments seemed to improve survival.[65] The work by Reynolds et al[59-65] and the subsequent development of IMV by Kirby et al[66] have determined the course of infant-ventilator evolution to this very day. Not only did pressure controllers operated in a continuous-flow, time-triggered, pressure-limited, time-cycled mode seem to improve prognosis, but they were (and are) easier to design and less expensive to manufacture than other types of ventilators. The belief was fostered that pressure-limited ventilation decreased barotrauma because peak inspiratory pressure was decreased. However, as discussed above, this is an oversimplification that is not supported by scientific evidence.

Partly for the historic reasons mentioned earlier and partly for economic reasons, there is not much controversy over the preference of pressure controllers versus volume controllers in neonatal intensive care units—at least in the treatment of RDS. However, the use of inverse I-E ratios has fallen out of favor because it doesn't seem to improve oxygenation dramatically (with modern infant ventilators and in less severely-ill neonates), it promotes gas trapping and inadvertent PEEP, and it does not reduce morbidity and mortality.[67]

Some people believe that pressure controllers are superior to volume controllers because they can maintain a constant airway pressure in the face of leaks around uncuffed endotracheal tubes. The reasoning seems to be that constant pressure implies that the delivered volume remains constant. This, however, is a misunderstanding. Aside from the effects on tidal volume of changing lung mechanics during pressure-controlled ventilation, leaks at the tracheal level result in decreased pressures in the trachea[30] and, hence, can affect ventilation in the same manner as does volume-controlled ventilation. The problem is that the effect is masked during pressure-controlled ventilation.

Recently, there has been a resurgence of interest in pressure-triggering infant ventilators using esophageal pressure, inspiratory flowrate, and abdominal expansion as the trigger variables because they are more sensitive than airway pressure.[68-70] The belief is that in patient-triggered ventilation the infant's breathing attempts are synchronized with the ventilator, and thus the risks of pneumothorax and intracranial hemorrhage will be reduced and oxygenation will be improved.[71,72] Short-term effects of patient-triggered ventilation seem to include a reduction in oxygen requirement and an increase in ventilatory rate, but infants of less than 28 weeks gestational age do not seem to tolerate this mode of ventilation.[73]

Ironically, the real debate over volume- vs pressure-controlled ventilation is occurring in the pediatric-adult area. Pressure-controlled inverse-ratio ventilation (PCIRV) is being used to treat ARDS, yet the arguments about whether it works and how it works are essentially the same as those that have been put forth in the neonatal literature for years. It seems to me that proponents of PCIRV are discovering the same effects and making the same mistakes as did the early researchers in infant ventilation.[74] In our experience at Rainbow Babies and Childrens Hospital in Cleveland, pressure-controlled ventilation provided by the Siemens Servo 900C

ventilator seems to improve oxygenation and ventilation in older children with ARDS; but, to avoid causing gas trapping and inadvertent PEEP, we refrain from using I-E ratios much greater than 3:1 and frequencies above 20-30 breaths/min. Inadvertent PEEP is additive to applied PEEP, decreases tidal volume, is not obvious from routine airway-pressure measurements, and has no theoretical advantage over increasing the level of applied PEEP.[38]

High-Frequency Low-Pressure versus Low-Frequency High-Pressure Ventilation

The ventilator management strategy of Reynolds has come to be regarded as using relatively low frequency, relatively high pressure, and relatively long inspiratory times. Some authors[67,75] have reported high incidences of pneumothorax (up to 50%) using this regimen.

Another school of thought advocates the use of higher frequencies and shorter inspiratory times as a means of improving outcome. Three studies[76-78] have been particularly influential with respect to this approach; however, the study by Bland et al[76] did not have a control group, and the studies by Spahr et al[77] and Heicher et al[78] did not distinguish infants by disease. The problem with lumping all diagnoses together is that the beneficial effects of the ventilatory method in one illness may be masked by the adverse effects of the method in another illness.[79]

In reviewing these issues, Ramsden and Reynolds[38] put particular emphasis on gas trapping and inadvertent PEEP. The fraction of the tidal volume remaining in the lungs as a function of expiratory time can be expressed as:

$$\frac{\text{volume trapped}}{V_T} = e^{-t/\tau}, \qquad [21]$$

which is simply a rearrangement of the equation for lung volume during expiration given in Equation 18. Using published values for resistance and compliance,[80-83] Ramsden and Reynolds[38] estimate the time constant (τ) to be as short as 0.05 seconds for infants with RDS, as long as 0.25 seconds for infants with normal lungs, and up to 0.5 seconds for infants with chronic lung disease. They point out that ventilating a normal infant at a frequency of 100 breaths/min and an I:E = 1:1 will result in trapping 30% of the tidal volume in the lung at end-expiration. Secretions in the endotracheal tube can double respiratory-system resistance,[84] and consequently in this example trapped gas can increase to 50%. Another consequence of high frequencies can be that inhomogeneity of time constants throughout the lung may cause areas with long constants to be less well ventilated than areas with short constants.[38] Although there is some evidence that spontaneously breathing infants breathe rapidly to prevent airway closure during expiration,[85] attempts to achieve the same effect with a mechanical ventilator are difficult to measure. Ramsden and Reynolds[38] state that "the situation is quite unlike that of the spontaneously breathing infant whose lungs are liberally endowed with stretch receptors providing the feedback information necessary to modulate respiratory timing in accordance with the changing lung mechanics."

Morley and South[86] have countered with the argument that the short time constants of babies with RDS allow expiratory times as short as 0.15 seconds with only 5% gas trapping. Milner[87] has suggested that even a 13% reduction in tidal volume caused by gas trapping will be more than compensated for by the increased frequency and that a 13% increase in PEEP is inconsequential. Greenough et al[88] compared frequencies of 30, 60, and 120 breaths/min at constant $\bar{P}_{aw}$. They showed an increase in oxygenation and ventilation only at a rate of 120 breaths/min and only in babies who were not paralyzed (some infants in the study were paralyzed if they were judged to be actively exhaling against positive-pressure inflation). Both Sechrist and Bourns infant ventilators were used and showed different results.

In my opinion, patients who initially can be oxygenated and ventilated easily by manual ventilation and who do not have significant lung disease should be ventilated with a volume-controlled mode, tidal volume in the range of 5-6 mL/kg,[89] minimal PEEP (eg, 2-3 cm H_2O [0.2-0.3 kPa]), and no inspiratory hold. Theoretical work suggests that for a given tidal volume, an ascending-ramp inspiratory-flow waveform minimizes the work of distending the lungs (perhaps minimizing the risk

of barotrauma) and minimizes mean intrapleural pressure (minimizing the risk of hemodynamic compromise).[90,91] These patients may also be candidates for pressure-support ventilation with volume monitoring. It may be that for patients with normal lungs, the mode of ventilation has no clinically important effect on gas exchange.[92]

I believe that patients who have surfactant-deficient lungs or who are difficult to oxygenate with the ventilator strategy described should be managed by time-cycled, pressure-limited ventilation with delivered tidal volume measured. Although the technology to measure tidal volume is available and affordable (eg, Bear NVM-1 neonatal volume ventilator), many studies of infant ventilation are flawed because tidal volume was not controlled as the key variable. Lachmann[44] has proposed that ventilation be switched from volume-control to pressure-control when P_{aO_2}/F_{IO_2} is below 100 torr, peak airway pressure (with I:E = 1:1) is higher than 35 cm H_2O [3.4 kPa], and PEEP exceeds 8 cm H_2O [0.8 kPa]. Ideally, some measurement of FRC should be made, but this is more difficult. The tidal volume should be kept in the range of 5-6 mL/kg. Frequency should be no higher than required to maintain the desired P_{aCO_2}, and PEEP should be adjusted to maintain oxygenation at the lowest F_{IO_2}. Inspiratory time should initially be set just long enough to deliver the tidal volume (ie, so that a shorter inspiratory time decreases tidal volume and a longer time does not increase tidal volume). If oxygenation continues to be a problem, a trial of longer inspiratory times and possibly reversed I-E ratios can be used.[44] It may take as long as 24 hours for significant improvement to occur. The general approach to ventilating patients with acute lung injury should be, in short, use small tidal volumes and high PEEP rather than large tidal volumes and low PEEP.[93]

If the patient has life-threatening barotrauma in the form of PIE or bronchopleural fistula, high P_{aCO_2} despite all efforts to optimize ventilation, or if the mean airway pressure required to ventilate or oxygenate is above some predetermined threshold, then a trial of high-frequency ventilation is warranted. The idea here is to carry the small tidal volume-high PEEP approach to the extreme. This should be accomplished with a device that is designed for the task. Conventional ventilators may operate at frequencies up to 150 breaths/min (limited by an arbitrary FDA ruling), but their ability to increase minute ventilation as rate increases is questionable.[94] Based on our experience with high-frequency jet ventilation,[95-97] I would guess that an appropriate threshold for a trial of high-frequency ventilation would be at a pressure cost of oxygenation (defined as $\bar{P}_{aw}$ divided by the arterial-alveolar oxygen tension ratio [P_{aO_2}/P_{AO_2}])[98] equal to about 100 cm H_2O [9.8 kPa] (equivalent to a $\bar{P}_{aw}$ of 15 cm H_2O [1.5 kPa] and a P_{aO_2}/P_{AO_2} of 0.15). We have been successful with frequencies of 100-250 cycles/min and I:E fixed at about 1:3 (adolescents and large children need lower frequencies than do premature infants to prevent clinically important gas trapping; gas trapping should be suspected if a ventilator-parameter change seems to cause an increase in both P_{aO_2} and P_{aCO_2}). Pressure amplitude (ie, PIP – PEEP) is adjusted to obtain the desired P_{aCO_2} while mean airway pressure is adjusted (via PEEP) to control oxygenation at the lowest F_{IO_2}.

The underlying philosophy in both scenarios is to maintain open alveoli throughout the ventilatory cycle by using $\bar{P}_{aw}$ as an index of mean lung volume and then to use either a small-to-normal tidal volume for compliant lungs or a very small tidal volume for noncompliant lungs at high risk for overdistention. The selection of frequency is a secondary consideration. With normal tidal volumes, normal frequencies can be used to maintain ventilation and gas trapping will be minimal. At small tidal volumes, higher frequencies will be necessary and, although gas trapping will undoubtedly occur, it should not greatly affect FRC.

I believe that these recommendations can be generalized to older patients and to other modes of ventilation. For example, the use of large tidal volumes (10-15 mL/kg) during volume-controlled SIMV has been questioned in a recent study by Lee et al.[99] They have pointed out that the belief in large tidal volumes to prevent atelectasis is based on studies of paralyzed, anesthetized patients on zero PEEP.[100] In contrast, many patients in pediatric intensive care units are awake, spontaneously breathing, and receiving PEEP. Lee et al[99] showed that adults randomized to mechanical ventilation with tidal volumes of 6 mL/kg had shorter

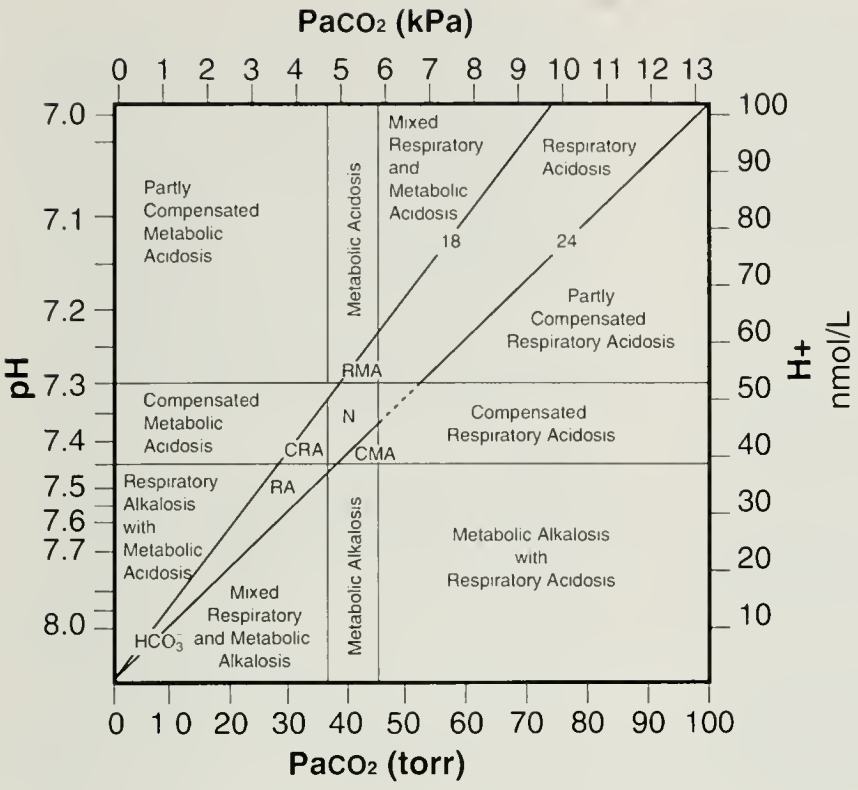

Fig. 17. Acid-base map for neonates. RMA is mixed respiratory and metabolic acidosis, N is normal acid-base status, CRA is compensated respiratory alkalosis, CMA is compensated metabolic alkalosis, and RA is respiratory alkalosis.

durations of intubation and decreased lengths of stay in the intensive care unit than did patients randomized to ventilation with 12 mL/kg.

The Future

In the future it is probable that ways to optimize ventilator settings for individual patients will be developed and general mechanical ventilation guidelines for specific populations will be formulated. One of the key variables in this process, FRC, is still difficult to measure at the bedside. In the near future, I envision technology built into the ventilator that will enable clinicians to evaluate FRC changes just as easily as compliance and resistance are evaluated today. These variables, along with hemodynamic measurements and continuous measurements of blood pH, P_{CO_2}, and P_{O_2} (perhaps with optodes) will provide the data necessary to make optimization of ventilator management more than somebody's experiential impression.

But, having the data is not enough. Indeed, at the present rate of technologic advance, the information available to the clinician will be overwhelming in quantity and diversity. To make sense of it all, we will need to incorporate the power of the microcomputer and artificial intelligence software. In my opinion, a clinician trying to ventilate a seriously ill patient is analogous to someone facing a world-class chess player. Each game, as each patient, is different. Yet the player who has studied the opening, midgame, and endgame move patterns recorded in detail over hundreds of years of experience will fare much better than someone who only knows how to move the pieces. Better yet, someone who has a computer with these patterns built into an artificial intelligence program customized for chess will not only fare well but will succeed over all but the most advanced opponents.

There is no reason why this strategy cannot be applied to the intensive care unit. Work at Rainbow Babies and Childrens Hospital[101] has shown that using a computerized algorithm for managing infant ventilation can be more effective than depending upon ad hoc human decisions. In essence, the program represents the condensed knowledge of practitioners and researchers with many years of collective experience. Ventilator changes are based on blood-gas interpretations as defined by a cus-

tomized 'blood-gas map' (Fig. 17).[98] Miller[102] has described a similar program for volume-controlled ventilation. I believe that further progress in optimizing conventional ventilation will only come about as the result of competition between clinical algorithms, with the prize being the lowest morbidity and mortality at the lowest cost. The winners of this contest will be our patients.

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97. Carlo WA, Siner B, Chatburn RL, Robertson S, Martin RJ. Early randomized intervention with high-frequency jet ventilation in respiratory distress syndrome. J Pediatr (in press).
98. Chatburn RL, Carlo WA. Assessment of neonatal gas exchange. In: Carlo WA, Chatburn RL. Neonatal respiratory care. 2nd ed. Chicago: Mosby-Year Book, 1988:40-60.
99. Lee PC, Helsmoortel CM, Cohn SM, Fink MP. Are low tidal volumes safe? Chest 1990;97:425-429.
100. Bendixen HH, Hedley-White J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. N Engl J Med 1963;269:991-996.
101. Carlo WA, Pacifico L, Chatburn RL. Efficacy of computer-assisted management of respiratory failure in neonates. Pediatrics 1986;78:139-143.
102. Miller PL. Goal-directed critiquing by computer: Ventilator management. Comput Biomed Res 1985;18:422-438.

Chatburn Discussion

Jobe: Several of your slides make the point that one of the unique aspects of the developing lung is that the dead space is not constant—in contrast to traditional teaching in pulmonary mechanics. Ventilation of preterm infants with high pressure causes airway distortion and, with time, loss of elasticity and airway dilation resulting in variable dead space during the respiratory cycle.[1] Often the measured minute ventilation for preterm infants will be very high, but the alveoli are collapsed such that most of the minute ventilation is dead space ventilation that does not result in gas exchange. We have no way to separate dead space from alveolar ventilation in preterm infants clinically by the pulmonary mechanics measurements available today.

1. Bhutani VK, Shaffer TH. Time dependent tracheal deformation in fetal, neonatal and adult rabbits. Pediatr Res 1982;16:830-833.

Green: Rob (Chatburn), consider oxygenation, ventilation, and complications as outcome variables and ventilator settings as input variables. Has anyone looked at perturbing the ventilator settings, looking at changes in the outcome variables in terms of ventilator settings, and by iteration in a systematic way optimizing ventilation for particular patients? Clinically, we do this in a somewhat less than algorithmic way all the time. I know you published an algorithm that you developed.[1,2] Has anyone a rigorous algorithmic approach for individual patients?

1. Chatburn RL, Carlo WA, Lough MD. Clinical algorithm for pressure-limited ventilation of neonates with respiratory distress syndrome. Respir Care 1983;28:1579-1586.
2. Carlo WA, Pacifico L, Chatburn RL, Fanaroff AA. Efficacy of computer-assisted management of respiratory failure in neonates. Pediatrics 1986;78:139-143.

Chatburn: Yes, I'm aware of some studies that have approached that. Lachmann,[1] for example, did that when he compared volume-controlled ventilation to pressure-controlled ventilation and very systemically looked at specific changes—I-E ratio and tidal volumes—and tried to find some optimal outcome in terms of ventilation and oxygenation. From that, he believes that pressure-controlled ventilation is better. I think most of the studies at least in neonatal literature are flawed in that they did not control for tidal volume. And going one step further, I don't think there are studies—it may not be possible to design studies—to really get at the question of outcome in terms of duration of ventilation, duration of stay in the ICU, or duration of high levels of F_{IO_2}. And I think that will only come when we can integrate all the data that are available to us in the form of artificial intelligence programs. I know that some ventilator manufacturers are doing this. I think what it's going to get down to is a battle of the algorithms—just as they have in chess. They have developed various artificial intelligence programs for chess—they battle it out to see who is the best. And I think that's the only way we are going to be able to manage the wealth of data that are available.

1. Lachmann B, Jonson B, Lindroth M, Robertson B. Modes of artificial ventilation in severe respiratory distress syndrome: Lung function and morphology in rabbits after washout of alveolar surfactant. Crit Care Med 1982;10:724-732.

Salyer: That was an excellent talk, Rob. Only one thing confuses me about your remarks. If in fact it's the volumetric expansion of the lungs that causes barotrauma, then all the other wonderful discussions aside, wouldn't it be better to have a volume-controlled basis for ventilation in the NICU—if in fact in your pressure-controlled approach, tidal volume could change significantly in the face of rapidly changing lung compliances?

Chatburn: Absolutely. The point I was trying to make in my talk was that you want to have the volume delivered early in inspiration and maybe hold the lungs open so that you can have a better distribution of ventilation. You can do that with pressure-controlled ventilation, but you have to monitor tidal volume because it's an indirect variable and you have to change the ventilator settings if lung mechanics change. You can do the same thing if you design the ventilator to control volume but deliver an exponential waveform rather than the more conventional ramp waveform. And, in fact, Siemens has a new ventilator with a mode called pressure-regulated, volume-controlled ventilation that I think does exactly this. The advantage of this mode is that because volume is being controlled rather than pressure, the level of ventilation stays constant if lung mechanics change.

However, I can foresee that clinicians will have difficulty understanding this new mode because the classification terminology they use is outdated. They are not accustomed to focusing on a control variable (like pressure, release, or flow) and realizing that in theory, a ventilator can select any one of them and deliver any waveform on a breath-by-breath basis. In fact, most clinicians don't think in terms of waveforms at all. They do not see that during pressure-limited, time-cycled ventilation, a rectangular pressure waveform will result in an exponential volume waveform. Therefore, it is difficult for them to conceive that by controlling volume instead of pressure and creating an exponential volume waveform, a rectangular pressure waveform will result—with the same potential benefits as pressure-controlled ventilation. I have introduced a new classification system in my talk and elsewhere[1] in order to accommodate the rapidly changing ventilator technology.

1. Chatburn RL, Lough MD. Handbook of respiratory care. 2nd ed. Chicago: Year Book Medical Publishers, 1990:191-223.

Martin: It seems to me that patient-triggered respirators have been around for quite a long time. How do the newer techniques differ from the old systems?

Chatburn: Well, in my experience, they weren't very good systems. They weren't very good at sensing the patient's respiratory efforts with a few exceptions. Maybe the old LS-104 was fairly good, but that was again mixing apples with oranges because that was volume control—not pressure control. There were to my knowledge no good pressure-control ventilators that had offered pressure triggering suitable for neonates. The reason was that you had a continuous-flow IMV circuit and you couldn't sense a pressure drop when the patient inspired. Perhaps the sensor technology was not sufficiently developed. But the trend now in new technology is to have very small pneumotachs that can be placed at the endotracheal tube as an inspiratory sensor rather than a flow-triggering mechanism. Such a device has been used on the Draeger Babylog 8000 ventilator. The Infrasonics Corp has come out with a different approach—a motion sensor that fits on the abdominal wall that triggers inspiration in response to the baby's inspiratory efforts.

Andersen: If you return to Lachmann's story,[1] what he did essentially was that he looked at three different parameters at the same time. First of all, he used pressure-controlled ventilation, but I think it's important to say that the pressure control he used was real pressure control and not the pressure control that we're accustomed to on the old ventilators. That's one thing, and the other thing is that he always would use a decelerating inspiratory flow pattern. The final thing is that he would reverse the I-E ratio demonstrating all three to be important.

1. Lachmann B, Danzmann E, Haendly B, Jonson B. Ventilator settings and gas exchange in respiratory distress syndrome. In: Prakash O, ed. Applied physiology in clinical respiratory care. The Netherlands: Martinus Nijhoff, 1982:141-176.

Chatburn: I think what you're saying is that they used a rectangular pressure waveform versus a triangular pressure waveform as would have been seen in the early days when using a Puritan-Bennett PR-2. The PR-2 is typically pressure-cycled versus current infant ventilators that are time-cycled and pressure-limited. Here again, we see the importance of terminology.

Andersen: Which might also recruit lung periphery and keep it open during expiration.

Chatburn: Exactly.

Hazinski: There was an article about a year or so ago in Lancet by Delpi and Parker who were with EOR Reynolds from MIT who used the diaphragm EMG to trigger the ventilator. It was remarkably effective.

It seems to me that just as important as determining how good the blood gases are is determining what these forms of ventilation do to pulmonary blood flow. Is there any consensus about the relative effects of volume-controlled ventilation vs pressure-controlled ventilation on capillary or blood vessel compression and vascular resistance? Some cardiac surgeons, for example, will not put a patient on a pressure-controlled ventilator because they believe that pressure-controlled ventilators increase pulmonary capillary resistance.

Chatburn: They're right, and I think that one of my slides showed that

pressure-controlled ventilation with a rectangular pressure waveform and the same tidal volume would give you a greater mean airway pressure. A greater mean airway pressure may lead to increased pulmonary vascular resistance and decreased pulmonary blood flow, especially in patients with normal lung compliance because airway pressure is more readily transmitted to the pulmonary vasculature.

Barnes: Rob (Chatburn), you said that those caring for adults had a lot to learn from those using pressure control and inverse I-E ratios with neonates. What message can you pass on for adult care based on your experience with neonates?

Chatburn: Well, I think the major concerns here are that extreme inverse I-E ratios are probably not going to be good for adults for the same reason they weren't really good for neonates. Clinicians need to understand the concept of time constants and their relevance to the phenomenon of gas trapping. Gas trapping is known not to be good in neonates because it gives you an occult decrease in alveolar ventilation—and the same thing happens with adults. For example, people have been pushing inverse-ratio pressure-control ventilation. Some authors say that gas trapping is good, but, theoretically, decreasing expiratory time to the point that we have gas trapping is no better than applying PEEP, in my opinion and may be worse because it is harder to control. Do we have a quick comment, Jens (Andersen)?

Andersen: The reason why inverse-ratio ventilation is used to a certain extent in adults now is that when you use inverse-ratio ventilation you actually want to create gas trapping. As long as you know what you're doing with your inadvertent PEEP and you measure your auto-PEEP. And, if you measure your auto-PEEP, and decrease that set PEEP level, then you can actually apply some of the PEEP you want to give to the patient by inversing the I-E ratio. This might create a nonuniform PEEP distribution in the periphery.

Chatburn: Well, I guess my only argument is: What is the theoretical difference between inadvertent alveolar PEEP and applied alveolar PEEP? It's the same PEEP in the lung, and my argument would be that inadvertent alveolar PEEP is too variable, too subject to changes in the pulmonary mechanics. You can't see it unless, as you say, you are constantly monitoring gas trapping, and somebody has got to be there to do that.

Andersen: I agree with you, but the important point then is that if you use inversed I:E to create PEEP, your peak pressure will automatically drop.

Chatburn: Well, six of one and half a dozen of the other. You have the same alveolar tidal volume either way.

Andersen: Maybe.

Chatburn: We could probably argue that forever.

Neonatal and Pediatric High-Frequency Ventilation: Principles and Practice

Carl H Coghill III MD, James L Haywood MD,
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Introduction

Assisted ventilation has contributed to a substantial reduction in mortality in infants with respiratory distress, but its use has been complicated by high morbidity. Pulmonary air leaks occur in approximately 24% of all infants requiring assisted ventilation.[1] From 25% to 33% of very-low birthweight infants who survive develop bronchopulmonary dysplasia.[2,3] Assisted ventilation can also adversely affect cardiac function.[4] Although the precise pathophysiologic mechanisms underlying these forms of lung injury have not been determined, high ventilatory pressures and the resultant barotrauma are thought to be major contributing factors. Furthermore, some infants still die with intractable respiratory failure despite the use of currently available conventional ventilators. Ventilators are needed that can improve gas exchange while minimizing barotrauma in these patients. Various high-frequency ventilators have been used successfully when conventional ventilators have failed to maintain adequate blood gases. Because high-frequency ventilation (HFV) may maintain adequate gas exchange at low airway pressures and thus lessen the likelihood of barotrauma, an increased interest in these new modes of ventilation has emerged.

During conventional ventilation (CV), the delivery of a normal tidal volume (V_T) to a noncompliant lung necessitates high inflating pressure. To diminish this problem, various systems capable of delivering HFV have been developed. With these ventilators, adequate gas exchange can be maintained with markedly reduced volumes delivered at high frequencies. If accompanied by decreased inflating pressures, HFV may result in a reduction in barotrauma. Recent data from our own and other institutions indicate that, when compared to CV, short-term HFV maintains adequate gas exchange in critically ill neonates, usually at lower airway pressures.[5-23] However, controlled clinical trials have not uniformly demonstrated clear advantages of HFV over CV.

Milestones in Infant and Pediatric HFV

In 1959, JM Emerson, patented a device that, by vibrating air into the patient's lungs, had the potential for enhancing gas exchange.[24] Subsequently, Sjöstrand reported his groups' modification of standard conventional ventilators to allow their use at frequencies of 60-120/min.[25] In 1974, Heijman and Sjöstrand first reported the application of HFV to neonates with respiratory distress syndrome (RDS).[5] Many reports of rescue use of HFV in neonatal and pediatric patients followed. Most recently, controlled trials have been performed. This review addresses these reports.

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Abbreviations Used in This Paper

CPAP	— Continuous positive airway pressure
CV	— Conventional ventilation
F_{IO_2}	— Fractional inspired oxygen concentration
HFOV	— High-frequency oscillatory ventilation
HFPPV	— High-frequency positive-pressure ventilation
HFV	—High-frequency ventilation
HFFI	— High-frequency flow interrupters
I:E	— Inspiratory-to-expiratory-time ratio
IMV	— Intermittent mandatory ventilation
P_{aCO_2}	— Arterial carbon dioxide tension
P_{aO_2}	— Arterial oxygen tension
$\bar{P}_{aw}$	— Mean airway pressure
PEEP	— Positive end-expiratory pressure
PIE	— Pulmonary interstitial emphysema
PIP	— Peak inspiratory pressure
RDS	— Respiratory distress syndrome
$\dot{V}_E$	— Expired minute ventilation
V_T	— Tidal volume

Classification of High-Frequency Ventilators

A number of high-frequency ventilators, each with unique characteristics, have been developed, and classification is not an easy task. Circuits and delivery system designs also vary, and these may have a major impact on the functioning of a high-frequency ventilator. Furthermore, considerable overlap exists in the characteristics of the various types of HFV. In addition, the strategies employed with a high-frequency ventilator may also affect its efficacy. Nonetheless, for purposes of simplicity, we have attempted to classify and characterize the principal techniques presently employed to deliver HFV (Table 1).

High-frequency positive-pressure ventilation (HFPPV) usually employs standard conventional ventilators modified with low-compliance tubing and connectors so that adequate V_T can be delivered despite very short inspiratory times. This technique was developed by Sjöstrand and coworkers[25] in an effort to reduce cardiac side effects from assisted ventilation, but was also found effective in achieving normal blood gas values at reduced airway pressures. Today most conventional neonatal ventilators have been modified in a similar way, allowing their use at rates of up to 150/min. However, limitations with this mode of ventilation have been observed. For example, as frequency is increased, tidal volume delivery may be so compromised that actual alveolar ventilation decreases despite an increase in minute ventilation ($\dot{V}_E$).[26]

High-frequency jet ventilation (HFJV) employs a high pressure source to deliver a volume of gas through a small-bore injector cannula. Delivered V_T may be large, but even volumes smaller than dead space can maintain normal CO_2 elimination.[27] Gas entrainment (the addition of gas from areas surrounding the jet-injector cannula to that intrinsically delivered by the jet ventilator) may oc-

Table 1. Techniques for High-Frequency Ventilation

	HFPPV*	Jet Ventilation	Flow Interruption	Oscillation
Tidal volume	> dead space	> or < dead space	> or < dead space	< dead space
Expiration	Passive	Passive	Passive	Active
Airway pressure waveform	Variable	Triangular	Triangular	Sine wave
Entrainment	None	Possible	None	None
Frequency	60-150/min	60-600/min	300-1200/min	300-3000/min

*HFPPV = high-frequency positive-pressure ventilation.

cur under certain circumstances. Entrainment may occur because of the viscous shearing force that exists between moving and static layers of gas or because of the development of relative negative pressure near the jet injector. However, gas entrainment can only occur with ventilator settings and circuit and patient characteristics that allow high rates of flow. We have found in an animal model of neonatal lung disease that entrainment contributes only minimally to total $\dot{V}_E$.[28] Humidification of gases is particularly difficult during jet ventilation. Inadequate humidification has contributed to fatal tracheal lesions.[29] Because of the uncertain contribution of entrainment to total $\dot{V}_E$, the practice of humidifying the bias flow gases alone is not adequate.

Similar to jet ventilators, high-frequency flow interrupters (HFFI) provide small volumes delivered at high frequencies by interrupting a flow or high-pressure source.[10] In contrast to jet ventilation, no injector cannula and no gas entrainment are present. High-frequency oscillatory ventilation (HFOV) is a unique form of high-frequency ventilation because expiration is active.[9,30] Delivered volumes are usually very small (even less than dead space) and frequencies very high (up to 3,000/min). Volume delivery and active expiration are achieved by a piston pump or acoustic speaker. Because expiration is active, shorter expiratory times can be used, and gas trapping may be less of a problem. Extensive laboratory research has been performed using HFOV, but clinical trials have been limited.

HFV has been used to apply pressure changes externally to the chest wall.[31] This modification could avoid upper-airway and parenchymal damage associated with endotracheal intubation. External high-frequency oscillations improve blood gases in normal and surfactant-deficient adult cats.[31] This technique is reminiscent of the negative-pressure ventilators that were successfully used in neonates with RDS in the past. New modifications may facilitate effective ventilation through the application of pressure changes to the chest wall without the previously encountered problems (frequent interruptions, leaks). However, this technique has not been tested in human neonates.

Despite many differences, the various high-frequency ventilators share many functional characteristics. An in-vitro evaluation[32] of eight commercially manufactured neonatal high-frequency ventilators (including HFJV, HFFI, and HFOV modes) revealed that, independent of the ventilator type, delivered tidal volume decreased with increasing ventilatory frequencies or decreasing endotracheal tube size but was relatively insensitive to lung compliance.

Gas Exchange during High-Frequency Ventilation

Because adequate gas exchange can occur at V_{TS} smaller than dead-space volumes, mechanisms other than bulk (convective) gas transport must be involved. Gas transport by convection occurs during HFV if V_{TS} larger than dead-space volume are employed. However, alveoli located close to the airway get direct ventilation at V_{TS} smaller than dead-space volume. Direct ventilation is not restricted to HFV, because it is well known that some CO_2 elimination occurs during spontaneous breathing at very small V_{TS}. A mechanism called pendelluft (the exchange of gas among lung units with different time constants), may account for some of the gas exchange that occurs even when V_{TS} are smaller than dead-space volume. Photographic[33] and asymmetric alveolar pressure[34] data support the existence of this mechanism of gas exchange during HFV.

Other mechanisms may also explain the enhanced gas exchange during HFV. However, less evidence for their existence is available. Gas velocity is higher in the center of the airway, and velocity profiles differ during inspiration and expiration. This mechanism (called streaming) effectively reduces dead space because gases in the center of the airways move preferentially forward while the marginated dead-space volume has a net backward movement.[35] Turbulence due to high-frequency velocity fluctuations and augmented diffusion may also enhance gas exchange during HFV. It is unclear which of these mechanisms of gas transport occurs with each of the modes of HFV and what relative effect these mechanisms have in improving

gas exchange. Furthermore, it is also unknown whether the importance of these mechanisms is determined by the mechanical properties of the respiratory system or the disease process.

Carbon Dioxide Elimination

The most consistent observation about gas exchange during HFV is that CO_2 elimination is usually easily accomplished. Most rescue and controlled trials have reported that a decrease in P_{aCO_2} follows the use of HFV. The improved CO_2 elimination is in part due to the increased $\dot{V}_E$ that HFV allows. In addition, V_Ts smaller than dead space may be sufficient for adequate gas exchange to occur during HFJV[27] and HFOV[30,36] However, CO_2 elimination during both HFJV[30] and HFOV[37] is predominantly determined by tidal volume rather than by frequency. Because it is usually difficult in the clinical setting to measure tidal volume during HFV, CO_2 elimination is achieved by adjusting pressure amplitude difference between peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) (Fig. 1).[38] Although CO_2 elimination is easily accomplished with most forms of HFV, caution should be exercised to prevent gas trapping because this may cause paradoxic CO_2 retention.[27]

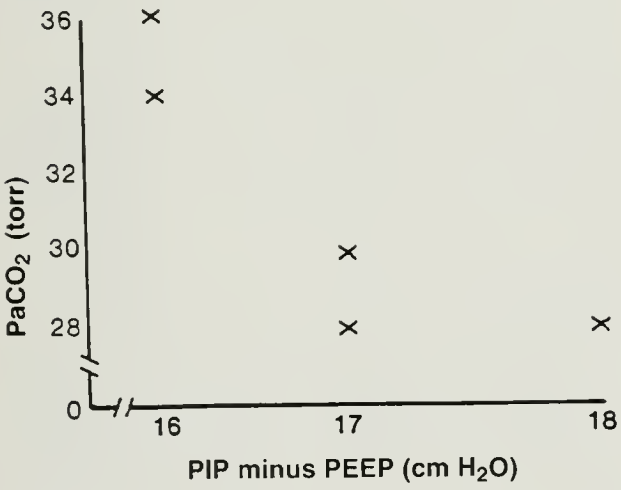

Fig. 1. The effect of pressure amplitude (difference between peak inspiratory, PIP, and positive end-expiratory pressure, PEEP) on P_{aCO_2} in an infant with RDS during HFJV. Pressure changes were performed in random order. P_{aCO_2} decreased as pressure amplitude was increased. (Reprinted, with permission, from Reference 38.)

Oxygen Uptake

Reports on the efficacy of oxygenation during HFV are mixed. Understanding of oxygenation is not as well defined as that of CO_2 elimination: increases, decreases, or no changes in oxygenation have been reported during HFV. However, initial studies paid little attention to mean lung volume and mean airway pressure ($\bar{P}_{aw}$). As with CV, studies have shown that during HFV, oxygenation is largely determined by $\bar{P}_{aw}$ (Fig. 2),[38] and the maintenance of an adequate lung volume.[9] Accordingly, maneuvers that recruit lung volume also improve oxygenation.[39] However, overdistention and gas trapping (for example, with very high $\bar{P}_{aw}$) cause ventilation-perfusion mismatch and impair oxygenation.

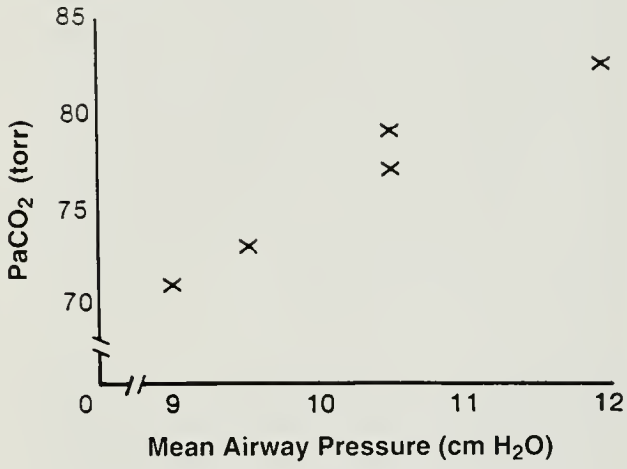

Fig. 2. The effect of $\bar{P}_{aw}$ on P_{aO_2} during HFJV on the same infant as in Figure 1. Pressure changes were performed in random order. P_{aO_2} improved as $\bar{P}_{aw}$ was increased. (Reprinted, with permission, from Reference 38.)

Clinical Experience with High-Frequency Ventilation

Respiratory Distress Syndrome and Respiratory Failure

High-Frequency Positive-Pressure Ventilation. Heijman and Sjöstrand[5] developed the first prototype of HFPPV for neonates. Using frequencies of 60 to 90/min, they successfully ventilated 3 of 5 ne-

onates who had RDS. Subsequently, Bland et al[6] modified conventional pressure- or volume-limited ventilators to attain rates of 60-110/min, and adequately ventilated 24 preterm infants with RDS (average birthweight 1,244 g) throughout the period that they required assisted ventilation. Despite the low birthweight and immaturity of these infants, a high percentage (92%) of them survived.

Following these observations, controlled studies were carried out to determine whether HFPPV was superior to CV. Boros and Campbell[7] performed a controlled, crossover study comparing HFPPV at rates of 66 ± 10/min versus "low-frequency, high-tidal volume" in 10 neonates with severe lung disease, mostly RDS. Improved CO_2 elimination was noted during the period of HFPPV. Although these investigators observed a fall in P_{aO_2} during HFPPV, an inadvertent reduction in $\bar{P}_{aw}$ occurred. In a large controlled trial of neonates with RDS or pneumonia (51 patients), Heicher et al[8] demonstrated that HFPPV markedly decreased the incidence of pneumothorax while PIP was reduced. Other studies have more recently confirmed that adequate gas exchange may be achieved with HFPPV in critically ill neonates.[14,15,21] It should be noted that many neonatal studies have reported the use of conventional ventilators at rates above 60/min, but have not used the term HFPPV.

High-Frequency Jet Ventilation. In 1983, Pokora et al[11] reported the first use of HFJV in 10 neonates with respiratory failure. These investigators employed rates of 260 ± 50/min and observed a reduction in the alveolar-arterial P_{O_2} gradient and P_{aCO_2} during HFJV as compared to CV. However, their success was adversely affected by the development of necrotizing tracheobronchitis and fatal tracheal obstruction. In a larger group of patients treated by this group of investigators, 44% of the infants developed tracheobronchitis.[16]

We used a jet ventilator in a crossover study of 12 infants with RDS who were ventilator dependent to determine whether a short period of HFJV allowed reduction of airway pressures.[12] Each infant was studied on CV prior to and after a 1- to 3-hour period of HFJV. A rate of 250/min was employed at an I-E ratio of 1:3 to 1:4. Average PIP decreased from 29 ± 3 cm H_2O during CV to 20 ± 4 cm H_2O during HFJV, and $\bar{P}_{aw}$ decreased from 14 ± 3 to 10 ± 2 cm H_2O. Despite attempts to maintain normocapnia (according to the protocol), a simultaneous decrease in P_{aCO_2} was seen from 39 ± 4 to 34 ± 4 torr with the use of HFJV. P_{aO_2}, PEEP, and cardiovascular parameters did not change. These data indicate that short-term HFJV maintains or improves gas exchange in infants with RDS despite a reduction in airway pressures. These short-term effects of HFJV on gas exchange have been confirmed by others.[18]

To determine whether these effects are long-lasting and whether they result in reduced barotrauma, 40 ventilator-dependent infants with RDS were randomized to receive either CV exclusively or HFJV for a period of 48 hours with subsequent return to CV.[20] Despite comparable oxygenation in both groups, infants treated with HFJV had lower P_{aCO_2} and $\bar{P}_{aw}$, confirming the initial observation that CO_2 elimination is enhanced by HFJV despite reduced airway pressures. Furthermore, bronchoscopies did not reveal evidence of necrotizing tracheobronchitis or bronchial obstruction following HFJV. From this study it was concluded that HFJV can be used effectively in the ventilatory management of neonates with RDS, without an increase in the incidence of side effects. Even though some complications of barotrauma (eg, air leaks) were decreased by 50%, the sample was too small to establish a statistically significant effect.

Gonzalez et al[22] using HFJV have confirmed these observations in 6 neonates with persistent gas leaks through thoracotomy tubes. They also demonstrated that the flowrate of the air leak decreased markedly at the same time that HFJV allowed a reduction in the $\bar{P}_{aw}$. Thus, HFJV may reduce flow through a bronchopleural fistula and promote its healing.

We have recently finished a randomized study of 42 patients that addressed the question of efficacy of HFJV during a prolonged ventilatory course.[40] In this study, infants randomized to HFJV were ventilated exclusively with jet ventilation for as long as a ventilator was required (up to 28 days). Separate sequential analyses were performed for mortality, air leaks, bronchopulmonary dysplasia, and intraventricular hemorrhage. Crossover and a combined analysis were performed, with death overriding

other outcome variables. Enrollment was completed when the combined analysis reached the sequential design boundary indicating no treatment difference (Fig. 3). In support of short-term studies, P_{aCO_2} was lowered by HFJV while $\bar{P}_{aw}$ was reduced. Despite the improved gas exchange during HFJV, neither bronchoscopy nor clinical course revealed an increase in airway complications. Despite the optimism from earlier research reports, this relatively small study suggests that early use of HFJV does not prevent or substantially reduce mortality or morbidity associated with assisted ventilation, even though short-term benefits in gas exchange and airway pressures occur. Mortality (19% in HFJV vs 24% in CV) and the incidence of air leaks (48% vs 52%), bronchopulmonary dysplasia (39% vs 41%), intraventricular hemorrhage (33% vs 43%), and crossover (14% vs 24%) did not differ significantly between the treatment groups. Crossover criteria were defined as a $P_{aO_2} < 50$ torr or respiratory acidosis with pH < 7.25 for two consecutive blood gas determinations despite increased ventilatory support when F_{IO_2} was 1.0 and $\bar{P}_{aw}$ was ≥ 18 cm H_2O.

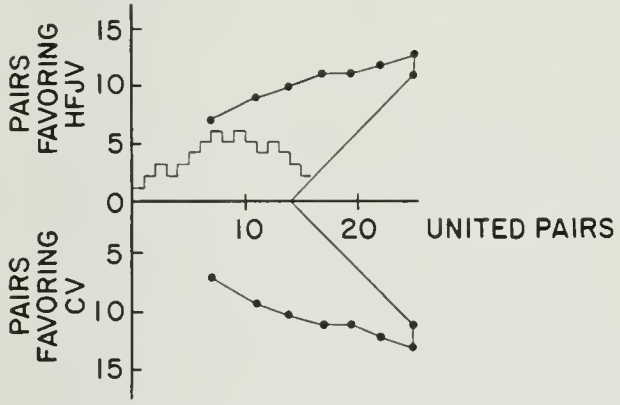

Fig. 3. Sequential analysis of combined outcome measures including mortality, air leaks, bronchopulmonary dysplasia, intraventricular hemorrhage, and crossover. The abscissa indicates the number of untied pairs. The study was completed when the boundary indicating no difference was reached. (Reprinted, with permission, from Reference 40.)

A report[41] on two groups of patients treated with the Bunnell Life Pulse Ventilator at multiple institutions across the United States has been published. Neonates were treated with HFJV if severe respiratory failure was unresponsive to CV. A control group was not studied. Data from the initial group of 92 neonates confirmed the observation from smaller trials that HFJV permitted a reduction in $\bar{P}_{aw}$ while P_{aCO_2} was improved. Unfortunately, 20 of 28 infants who died had evidence of tracheobronchitis, and the incidence of pneumopericardium was unexpectedly high. A second group of 108 patients was treated with an improved humidification system. When compared to the initial patients, neonates treated in this second phase had a reduced incidence of necrotizing tracheobronchitis and pneumopericardium, improved survival, and a reduction in the incidence of pulmonary interstitial emphysema (PIE). The improved outcome opened the door for further controlled clinical trials with this ventilator.

Recently, the preliminary results of a multicenter controlled trial of HFJV in neonates with PIE have been reported.[42] Keszler et al randomized 144 neonates who developed interstitial emphysema during the first week of life to treatment with HFJV or with "rapid rate CV." Resolution of PIE and improvement of emphysema with reduction in airway pressures was used as success criteria. Forty-six HFJV neonates (61%) met success criteria compared to 25 CV infants (38%). Success criteria were met by more patients crossed over from CV to HFJV than vice versa (43% vs 9%). Mean and peak pressure decreased, and P_{aCO_2} improved in the HFJV group. No increase was seen in the incidence of tracheal lesions or other complications previously reported with HFJV. However, despite these observations, mortality, air leaks, bronchopulmonary dysplasia, and other complications of CV were not reduced in the HFJV group.

We have also used HFJV in neonates with persistent pulmonary hypertension who met established criteria for a high predicted mortality.[43] Fourteen neonates who had severe respiratory failure and hypoxemia during CV received HFJV, while 23 comparable infants were treated exclusively with CV. Initiation of HFJV resulted in reduction of $\bar{P}_{aw}$ and P_{aCO_2}, but oxygenation did not improve. Furthermore, mortality and other complications of CV were not reduced with HFJV.

In summary, controversy persists regarding the advantage of and indications for HFJV in neonatal

respiratory diseases. Further clinical trials should determine whether HFJV results in improved outcome.

High-Frequency Flow Interruption. Frantz and co-workers[10] reported, in 1983, the application of HFFI at frequencies of 300-1200/min in 10 neonates with RDS and 5 with PIE. Gas exchange (both P_{aO_2} and P_{aCO_2}) was improved during HFFI at lower PIP, but $\bar{P}_{aw}$ could not be decreased. Even though this was an uncontrolled study, resolution of RDS and emphysema occurred in most infants. Gaylord et al confirmed that blood gases and airway pressures were improved by HFFI in neonates with PIE.[23]

High-Frequency Oscillatory Ventilation. In 1981, Marchak and co-workers[9] reported a crossover, controlled study in 8 neonates with RDS, using HFOV at rates of 480-1200/min for 1- to 4-hour periods. Oxygenation was improved during HFOV; but in 3 infants in whom airway pressure was measured, the increase in P_{aO_2} was found to depend on increases in $\bar{P}_{aw}$.

The National Institutes of Health sponsored a large multicenter trial to test the efficacy and safety of HFV in patients at risk for bronchopulmonary dysplasia.[44] After careful evaluation of commercially available high frequency ventilators, an HFOV ventilator (the Hummingbird) was selected for this trial. Premature infants less than 2 kg who required any ventilatory support were randomized to either HFOV or CV. HFOV was used at a fixed frequency of 900/min, and volume recruitment maneuvers were employed. In this well-designed study, the incidence of bronchopulmonary dysplasia was similar in the two groups (Table 2).

Table 2. Major Outcomes for the Multicenter HFOV Trial [40]*

	CV n = 346	HFOV n = 327	p value
Bronchopulmonary dysplasia	41%	40%	0.79
Mortality at 28 days	17%	18%	0.73
Air leak (any type)	38%	45%	0.05
Grade 3 and 4 IVH	18%	26%	0.02
Periventricular leukomalacia	7%	12%	0.05

* CV = conventional ventilation; HFOV = high-frequency oscillatory ventilation; IVH = intraventricular hemorrhage.

HFOV did not reduce mortality or the level of ventilatory support during the first 28 days of life. Furthermore, HFOV resulted in an increased incidence of air leaks, Grades 3 and 4 intraventricular hemorrhage, and periventricular leukomalacia. These results indicate that HFOV, as used in this trial, offers no advantage over CV in this patient population. It is possible that the use of HFOV in other patient populations or with other ventilatory strategies may yield different results. Recently, Clark et al[45] reported on the early use of HFOV in patients with severe RDS who were not failing CV. Eighty-one patients were randomized to one of three-groups: (1) CV for their complete clinical course, (2) HFOV followed by CV, and (3) HFOV for their complete clinical course. HFOV resulted in a reduction of bronchopulmonary dysplasia (68% vs 50% vs 42%), but did not reduce mortality or other complications of CV (air leaks and intraventricular hemorrhage). Furthermore, the incidence of bronchopulmonary dysplasia remained relatively high despite HFOV.

HFOV has also been used in neonates with persistent pulmonary hypertension. Kohelet et al[46] treated 41 infants with pulmonary hypertension and birthweights greater than 2.0 kg. HFOV improved blood gases despite a reduction in $\bar{P}_{aw}$. Although criteria for high predicted mortality were not used, only 5 infants died. Cornish et al[47] also used HFOV in 8 infants who met high mortality criteria ($A\text{-}aDO_2 > 600$ torr for 6 hours [8 patients]) and in 7 who had acute deterioration. Seven infants (only 2 of whom had met the $A\text{-}aDO_2$ criteria) improved with HFOV, and 6 of these patients ultimately survived without need for extracorporeal oxygenation. Infants who responded to HFOV tended to be those who qualified because of acute deterioration or, as in the HFJV study described, those who were smaller and more immature.

Bohn et al[48] used HFOV in 16 neonates with diaphragmatic hernia and severe hypoxemia. Both oxygenation and CO_2 elimination improved during HFOV. However, only two patients ultimately survived. As discussed before, present clinical trials do not support the widespread use of HFOV in neonatal patients. Further clinical trials will determine if these new ventilatory techniques improve neonatal outcome.

Combined HFV-Conventional Ventilation. Recently, several investigators have successfully combined HFV and intermittent mandatory ventilation (IMV) in patients with severe respiratory failure. Boynton et al[13] used an oscillator at a frequency of 1200/min combined with intermittent mandatory ventilation as a rescue in 12 neonates with respiratory failure despite CV. Oxygenation and CO_2 elimination were markedly improved with combined HFOV despite a reduction in $\bar{P}_{aw}$ and CV rate. Gaylord et al[23] used a modification of HFFI combined with CV in 9 preterm infants with severe PIE and also demonstrated improved gas exchange at lower $\bar{P}_{aw}$s and rates. HFJV (rates 300-450/min) was combined with CV in 11 preterm infants by Donn et al.[17] Adequate blood gases were maintained—also at lower $\bar{P}_{aw}$s than with CV. Combining HFV with intermittent mandatory ventilation consistently improves gas exchange and permits a reduction in $\bar{P}_{aw}$. The rationale behind the role of intermittent inflations is that they may prevent or resolve atelectasis that sometimes complicates prolonged periods of HFV, especially when very small V_Ts are employed.

Other Potential Clinical Uses of HFV

Bronchopleural Fistula and Pneumothorax. Pneumothorax is a frequent occurrence in neonatal ventilatory therapy. The study by Gonzalez et al[22] used HFJV in 6 infants who had severe pulmonary disease and persistent air leaks via thoracotomy tubes placed for pneumothoraces. When infants were treated with HFJV, the flow through the bronchopleural fistula decreased. Simultaneously, PIP and $\bar{P}_{aw}$ were decreased during HFJV while adequate gas exchange was maintained. This study confirms previous case reports describing similar observations in animals and adult patients. However, no data exist to indicate that HFV can prevent the development of air leaks. Animal data suggest that the reduced flow through a bronchopleural fistula may be due to the decreased $\bar{P}_{aw}$ that occurs with HFJV.[49]

Impaired Cardiac Function. Although several authors have reported worsening cardiac hemodynamics during HFV, the increased $\bar{P}_{aw}$ employed in those studies may have accounted for the adverse cardiac effects. Recent animal studies in which $\bar{P}_{aw}$ was comparable during HFV and CV have shown no change in cardiac output. In infants and children following cardiac surgery, cardiac output either improved or remained unchanged during periods of either HFFI[50] or HFJV.[51] Interestingly, cardiac output improved during HFJV in those infants who initially had poor cardiac output during CV. Regardless of the ventilatory mode, cardiac output was dependent on $\bar{P}_{aw}$. It is likely that the lower $\bar{P}_{aw}$ used during HFV may reduce the cardiovascular side effects of transpulmonary pressures.

Bronchoscopy and Airway and Thoracic Surgery. Because HFV allows adequate gas exchange with small V_T, it reduces airway and thoracic structure movement, which may facilitate surgical procedures. We have devised a system using a combination of jet ventilation and constant air suction, both of which deliver gas with a single interface valve that permits ventilation during bronchoscopy.[52] When tested in vitro and in rabbits with normal lungs, baseline functional residual capacity remained constant. This system also improved ventilation when performed simultaneously with bronchoscopy. If found to be applicable to neonates, this system should facilitate a safer and more complete visualization of the airways during bronchoscopy. HFV may also facilitate airway and thoracic surgery as excursions during ventilation are decreased.[53] When delivered transtracheally, HFJV may be an alternative mode of ventilation during cardiopulmonary resuscitation.[54]

Adult Respiratory Distress Syndrome. Although initial enthusiasm occurred with treatment of adult respiratory distress syndrome, a study in which 309 patients were randomized to receive either conventional ventilation or HFJV demonstrated that survival and total duration of intensive care stay was not altered by the ventilatory mode, despite the lower airway pressures required.[55] Nonetheless, with their extensive experience, these investigators reported few side effects and safe application of HFV.

Table 3. Comparisons of Neonatal High-Frequency Ventilation (HFV) Studies*

HFV Mode	Authors, Year	Frequency (cycles/min)	Patient Population	Study Design	Major Results/ Outcome
HFPPV	Heijman & Sjostrand,[5] 1974	60-90	5 with RDS	Uncontrolled	3/5 survived
	Bland et al,[6] 1980	60-90	24 with RDS	Uncontrolled	22/24 survived
	Boros & Campbell,[7] 1980	66 ± 10	10 with RDS	Controlled, crossover	P_{aO_2} decreased, P_{aO_2} dependent on $\bar{P}_{aw}$
	Heicher et al,[8] 1981	60	51 with RDS with pneumonia	Controlled	Pneumothorax and PIP decreased
	Field et al,[14] 1984	100	17 with RDS	Controlled, crossover	P_{aCO_2} decreased
	Eyal et al,[15] 1984	90-180	25 with respiratory failure	Uncontrolled	P_{aCO_2} decreased, P_{aO_2} increased 18/24 survived
	Sedin,[21] 1986	60-65	24 with RDS	Uncontrolled	23/24 survived
HFJV	Pokora et al,[11] 1983	260 ± 50	10 with respiratory failure	Uncontrolled	5/10 survived, tracheal obstruction in 3
	Carlo et al,[12] 1984	250	12 with RDS	Controlled, crossover	$\bar{P}_{aw}$ and P_{aCO_2} decreased
	Boros et al,[16] 1985	248 ± 42	34 with respiratory failure	Uncontrolled	11/34 survived, 10/12 tracheobronchitis
	Donn et al,[17] 1985	300 ± 450	11 with respiratory failure	Uncontrolled	3/11 survived
	Pagani et al,[18] 1985	250	9 with RDS	Controlled, crossover	$\bar{P}_{aw}$ and P_{aCO_2} decreased
	Carlo & Chatburn,[34] 1988	250	40 with RDS	Controlled, crossover	$\bar{P}_{aw}$ and P_{aCO_2} decreased
	Gonzalez et al,[22] 1987	420 ± 44	6 with pneumothorax	Controlled, crossover	$\bar{P}_{aw}$ and P_{aCO_2} decreased
	Bunnell,[31] 1988		92 with respiratory failure	Uncontrolled	$\bar{P}_{aw}$, PIP, and P_{aCO_2} decreased, 20/28 tracheobronchitis, increased pneumopericardium
	Bunnell,[31] 1988		108 with respiratory failure	Historic controls	No increase in tracheobronchitis or pneumopericardium
	Carlo et al,[43] 1989	212 ± 29	37 with respiratory failure	Historic controls	No reduction in mortality

Table 3. Comparisons of Neonatal High-Frequency Ventilation Studies, continued.

HFV Mode	Authors, Year	Frequency (cycles/min)	Patient Population	Study Design	Major Results/ Outcome
HFJV continued	Spitzer et al,[56] 1989	420	176 with respiratory failure	Uncontrolled	$\bar{P}_{aw}$ and P_{aCO_2} decreased, P_{aO_2} increased
	Keszler et al,[42] 1990	420	144 with PIE	Controlled, crossover	$\bar{P}_{aw}$ and P_{aCO_2} decreased, resolution of PIE
	Carlo et al,[36] 1990	250	42 with RDS	Controlled, randomized	$\bar{P}_{aw}$ and P_{aCO_2} decreased, no reduction in mortality or morbidity
HFFI	Frantz et al,[10] 1983	200-1200	8 with RDS/PIE	Uncontrolled	Resolution of PIE
	Gaylord et al,[23] 1987		9 with PIE	Controlled, historic controls	$\bar{P}_{aw}$ and P_{aCO_2} decreased, P_{aO_2} increased
	Pfenninger & Gerber,[57] 1987	600	8 with RDS	Uncontrolled	3/8 technical problems, P_{aO_2} improved
HFOV	Marchak et al,[9] 1981	480-1200	8 with RDS	Controlled, crossover	P_{aO_2} dependent on $\bar{P}_{aw}$, no reduction in $\bar{P}_{aw}$
	Boynton et al,[13] 1984	1200	12 with respiratory failure	Uncontrolled	$\bar{P}_{aw}$ decreased
	Bohn et al,[48] 1987	900	16 with diaphragmatic hernia	Uncontrolled	Blood gas values improved
	Cornish et al,[47] 1987	900	15 with respiratory failure	Uncontrolled	Reduced need for ECMO
	Kohelet et al,[46] 1988	900	41 with respiratory failure	Uncontrolled	36/41 survived
	HIFI Study Group,[44] 1989	900	673 prematures	Controlled, randomized	Increased air leaks, intraventricular hemorrhage, no reduction in BPD, no reduction in $\bar{P}_{aw}$
	Clark et al,[45] 1990		81 with RDS	Controlled, randomized	Reduction in BPD

* HFV = high-frequency ventilation.
HFPPV = high-frequency positive-pressure ventilation.
$\bar{P}_{aw}$ = mean airway pressure.
RDS = respiratory distress syndrome.
PIP = peak inspiratory pressure.
HFJV = high-frequency jet ventilation.
HFFI = high-frequency flow interruption.
ECMO = extracorporeal membrane oxygenation.
BPD = bronchopulmonary dysplasia.

Practice of High-Frequency Ventilation

We have selected three of the many ventilators in widespread use that represent the various types of devices.

High-Frequency Jet Ventilation. The Bunnell Life Pulse Jet Ventilator* is a pressure preset, time-cycled jet ventilator connected in parallel with a conventional infant ventilator and circuit. This ventilator is one of the high-frequency devices in widespread use in the United States at this time. It is approved for use in infants with ventilatory failure who develop an air leak.

Clinical application of this high-frequency ventilator requires a special triple-lumen endotracheal tube. The main lumen connects to the conventional ventilator in the usual way. Gas enters the patient airway via a jet injector port located proximal to the endotracheal tube tip. This jet ventilator operates at frequencies of 240-660/min, or 4-11 Hz, with a PIP range of 4-50 cm H_2O and an inspiratory time range of 0.020 to 0.035 seconds. Operator controls are provided for PIP, inspiratory time, and ventilatory frequency. Humidification is provided by a servo-controlled heater-humidifier.

Wide swings in pressure delivered to the airway can be narrowed with jet ventilation, while $\bar{P}_{aw}$ and lung volume are maintained at low V_Ts and the frequency of conventional intermittent mandatory ventilation (IMV) is reduced. However, low 'background' IMV (2-10/min) is recommended to maintain lung volume and prevent progressive atelectasis.

HFJV is started by imposing jet ventilation breaths at a rate of around 420/min at peak pressures of approximately 90% of the conventional PIP, with a jet inspiratory time of 0.02 seconds. The PIP on the conventional ventilator is usually kept at about 10 cm H_2O above the HFJV PIP. IMV is rapidly reduced over several minutes to the desired background rate. As IMV is reduced, $\bar{P}_{aw}$ may fall, and HFJV PEEP may have to be raised to maintain the $\bar{P}_{aw}$.

As with the other high-frequency ventilators, strategies for management of gas exchange with HFJV include maintenance of lung volume by means of various alveolar recruitment procedures and other ventilator setting changes. Management of adequate oxygenation depends upon maintenance of lung volume; so, any process that allows lung volume to fall (such as suctioning) may need to be followed by volume re-recruitment procedures. Conventional IMV rate and PIP can be temporarily increased for brief periods to restore volume.

Oxygenation is optimized by adjustments in $\bar{P}_{aw}$ and F_{IO_2} (Fig. 1). With lung underexpansion as in RDS, $\bar{P}_{aw}$ is augmented by increasing PIP, PEEP, frequency, or inspiratory time. Usually, PEEP is the variable adjusted upward, to raise $\bar{P}_{aw}$, if oxygenation is poor and ventilation is adequate. If oxygenation is poor and the lungs appear to be overexpanded, then excessive pressure or gas trapping should be suspected. In this situation, oxygenation might improve with reduction in $\bar{P}_{aw}$.

CO_2 elimination depends strongly on V_T (Fig. 2) and is somewhat affected by frequency.[27] V_T is determined by the pressure amplitude or gradient (PIP-PEEP). Decreasing PEEP or increasing PIP increases the pressure gradient and improves CO_2 elimination. If this fails to improve CO_2 elimination, an increase in frequency can be attempted.

Conversely, as ventilation improves and P_{aCO_2} falls, PIP is reduced, decreasing the pressure gradient. Once F_{IO_2} is less than approximately 0.7, PEEP is reduced as oxygenation improves. Once both HFJV and conventional ventilator PIP are below approximately 15 cm H_2O, only HFJV PIP is further reduced. Frequency is gradually reduced to around 360/min, and the patient can usually be extubated.

High-Frequency Flow Interruption. The Infant Star High-Frequency Ventilator is a computerized, pressure-limited, conventional ventilator with a solenoid-controlled flow interrupter that optionally delivers high-frequency ventilation between 'conventional' IMV breaths. Unlike most interrupters, an active expiratory phase is achieved through both an inertial effect and via maintenance of subambient pressures in the exhalation arm of the cir-

* Suppliers are identified in the Product Sources section at the end of the text.

cuit. These pressure differentials are produced with a jet venturi system near the exhalation valve and aid in creating the active expiratory phase. Thus, in some ways, the Infant Star High-Frequency Ventilator behaves as an oscillator and is appropriately considered as such by some clinicians and investigators. Pressure changes can be delivered over a wide range of frequencies, though little experience has been gained at frequencies < 10 or > 2 Hz.

The Infant Star's HFV component is approved for use in infants receiving CV who develop an air leak. The Infant Star is usually begun at a frequency of 600/min (10 Hz) with $\bar{P}_{aw}$ starting at the same level as with CV. Amplitude, reflected as a dimensionless number on a digital display, is adjusted until active vibration of the baby's chest is observed. This degree of chest expansion is usually sufficient to achieve adequate CO_2 elimination. IMV is reduced over a half-hour period to about 10/min, and $\bar{P}_{aw}$ is adjusted using the CPAP control knob.

CO_2 elimination is usually easily managed by adjustment of the amplitude; but to achieve a sufficient pressure gradient, it is necessary to have a minimal compressible volume in the ventilator circuit. To this end, a short, noncorrugated Tygon circuit is used in combination with a special humidification chamber constructed to minimize compressible volume.

Once oxygenation is adequate and F_{IO_2} is below approximately 0.7, $\bar{P}_{aw}$ is reduced by decreasing the CPAP (PEEP). Amplitude is adjusted downward (decreasing the HFV PIP) as P_{aCO_2} falls. When amplitude is minimal there will be no chest vibration. At this point, the baby is usually receiving minimal pressure support at low IMV, and HFV can be discontinued, and the baby can be extubated soon thereafter.

The Infant Star High-Frequency Ventilator is sensitive to endotracheal-tube internal diameter. Delivered pressure is proportionately attenuated by smaller tube diameters or by an obstruction, such as mucus plugging. We try to use the largest acceptable tube diameter and respond to sudden decompensations in ventilation or oxygenation by looking for obstruction of the tracheal tube.

High-Frequency Oscillatory Ventilation. The SensorMedics 3100 Oscillatory Ventilator is a true piston-pump oscillator. The active expiratory phase offers the theoretical advantage of preventing air trapping. Our experience with this device has found 900/min (15 Hz) to be the frequency at which most infants are ventilated best. $\bar{P}_{aw}$ and oscillatory pressure amplitude (referred to as power) are varied by increasing displacement of the piston. Inspiratory time of approximately 33% of the cycle (1:E of 1:2) is more commonly used. The piston pump creates a nearly square pressure waveform, which airway resistance (mostly in the endotracheal tube) attenuates to a more triangular form.

The strategy for ventilation of the infant at risk for air dissection takes advantage of the assumption that PIP is the cause of airway rupture. HFV can deliver a comparable $\bar{P}_{aw}$ and eliminate CO_2 at lower peak inflation pressures. Therapy is initiated, as with the Infant Star, by adjusting oscillatory pressure amplitude just high enough to produce visible chest-wall vibration. If maximal amplitudes do not improve CO_2 removal sufficiently, then frequency can be reduced from 900 to 600/min (15 Hz to 10 Hz). With frequency reduction, less attenuation of the amplitude occurs in the endotracheal tube, thus preserving a higher amplitude to the airway and lungs. If respiratory acidosis still does not improve with this maneuver, then inspiratory time can be increased toward 50%.

Oxygenation is managed by increasing $\bar{P}_{aw}$ to a level 10% above that used with conventional ventilation. As compliance improves, F_{IO_2} is reduced to approximately 0.7, then $\bar{P}_{aw}$ reduction is begun. When $\bar{P}_{aw}$ is down to 10 to 12 cm H_2O, amplitude is less than 30, and air leaks (if present) have resolved, the patient may tolerate weaning to conventional ventilation.

In summary, the practice of high-frequency ventilation is still in its infancy (Table 3). Not enough data exist to accurately predict which groups of infants will benefit,[56,57] although at this time it seems that the infant most likely to benefit is the tiny, ventilator-dependent infant at risk for air leak phenomena or the neonate who has already experienced air leaks. Further studies should delineate differences among the various high-frequency ventilators and their applications to clin-

ical practice and should open pathways into the investigation of iatrogenesis with the use of these new therapies.

PRODUCT SOURCES

Ventilator Circuit Tubing:
Tygon, Norton Co, Worcester MA

Ventilators:
Life Pulse Jet Ventilator, Bunnell Inc, Salt Lake City UT
Infant Star High-Frequency Ventilator, Infrasonics Inc, San Diego CA
SensorMedics 3100 Oscillatory Ventilator, SensorMedics Corp, Yorba Linda CA

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Carlo Discussion

O'Rourke: In one of his studies, de-Lemos and his group[1] took infants who met ECMO criteria and first offered them oscillation. About half of them improved with the oscillator and half went on to ECMO. The group that did well with the oscillator were those infants with fairly homogeneous lung disease (ie, pneumonia). The groups that did not do well had concomitant cardiovascular compromise. This suggests that some infants with persistent fetal circulation may in fact respond to HFV, but the response may be dependent on the primary, precipitating disease.

1. Carter JM, Gerstmann DR, Clark RH, et al. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 1990;85:159-164.

Carlo: Yes, I did not present those data because they are similar to our results. With jet ventilation, we found that premature babies with RDS were the infants who survived; whereas, meconium-aspiration babies did not survive.

Barnes: Did I hear you say that with high-frequency oscillation the frequency isn't that important? I think that some people believe that you need to use 15 Hz to get the effect you're looking for. I thought the slide that you showed said that tidal volume was more important than oscillation frequency?

Carlo: Maybe that's when I switched to Spanish. No, I didn't say that it was not important. I think that few studies have looked at high-frequency oscillatory ventilation. Most investigators use 15 Hz and think it is the best frequency because a strong effect of frequency has not been reported, whereas tidal volume markedly affects CO_2 elimination. So, it's just maybe a compromise in what's more important to change. And, even though we have found the effects of frequency sometimes necessary, we tend to prefer to make tidal volume changes as opposed to frequency changes.

Jobe: A significant difficulty with attempts to introduce new ventilatory techniques (such as oscillation and jet ventilation) is that we are still trying to learn how to use conventional ventilation in different disease states. The nonuniform application of conventional techniques makes interpretation of results in infants that have failed conventional techniques difficult. Also, there will be long and complex learning curves for the use of these new techniques in different patient populations. I was impressed at the Snowbird High Frequency Conference last year with the number of abstracts describing problems with the use of high-frequency equipment. The use of sustained inflation to achieve higher lung volumes followed by oscillation has been proposed as an optimal strategy to minimize lung damage.[1] However, without techniques to measure lung volume this strategy can be very dangerous because overinflation can be as damaging as underinflation.

1. McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant deficient rabbits. Am Rev Respir Dis 1988;137:1185-1192.

Carlo: That's a very good point, and I would like to comment on it because we really still don't know what is the best way to use a high-frequency ventilator. It has been demonstrated, for example, that sustained inflation improves oxygenation in surfactant-deficient lungs, and this might be very important with high-frequency ventilation.[1] Attempting to control lung volume introduces a very different way of thinking—maybe we ought to inflate their lungs to an appropriate lung volume and then ventilate with high-frequency ventilation, or maybe we should use higher inflating pressures.

1. Walsh MC, Carlo WA. Sustained inflation during HFOV improves pulmonary mechanics and oxygenation. J Appl Physiol 1988;65:368-372.

Salyer: Along the same avenue of thought, in the HIFI study[1] I wonder what the magnitude of differences was in how people used and controlled conventional mechanical ventilation from center to center. If you look at the data from center to center and break it out that way, are there in fact significant differences in the ability to prevent BPD using conventional versus high-frequency oscillation? By this I mean there tends to be enormous variation in conventional ventilator management between individual neonatologists, let alone between centers. Thus, it seems as if the control group in this study may not have been well controlled.

1. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88-93.

Carlo: Those data have been analyzed in every possible way. I would say there are important differences between an experiment and a clinical trial. In a controlled experiment in the laboratory, you control all the variables. In a clinical trial there are some things you cannot control, and because we cannot agree on how to use conventional ventilation, even within one institution, it would have been impossible to develop a strict study protocol to tell each of us how to do conventional ventilation.

Goldberg: The HIFI study is interesting in that there are center differences in terms of outcome. Some showed improvement, some a worsening, and in some no effect was noted using oscillation versus conventional ventilation. The aggregate statistics show no difference overall. What I find intriguing is that some of the centers with the most experience with high-frequency ventilation show higher rates of BPD using oscillation compared to centers with less experience. I think that we learned from the high-frequency ventilation study that we need to be cautious and to perform large multicenter studies to adequately evaluate new therapies.

Carlo: That's a very good point. With more than 10 hospitals, we could have written many individual papers. Two or three of the papers probably would have said that high-frequency oscillation was better than conventional ventilation—but two or three other papers would have said that it was worse. Just to make that point, I am agreeing of course with what Ron (Goldberg) is saying that this is a major advantage of a multicenter trial.

Goldberg: Just to re-emphasize this point, review the use of phenobarbital to prevent intraventricular hemorrhage in preterm infants. There are articles to show that it decreases, increases, or has no effect on the incidence of hemorrhage. If each center published its findings you might have the confusion of 10 articles and 3 possible outcomes.

Fanaroff: I think we're starting to lose the trees in the forest or something to that effect. I think what you're talking about with a big trial like that is avoiding the beta error that you don't avoid with small trials. In the individual trials that you showed us, there were differences but the baseline was all over the place. It's only when you start getting numbers in the 600 and 700s that you really answer a specific question as was outlined at the start of the study. And I think it's very disturbing that it was a major outcome that was negative. And the point that Alan Jobe made, I think, is a very telling one—the ventilator that was used during the study was one that nobody had any experience with and it was a learning curve going into the study.

Carlo: It was a new ventilator; however, the design of the ventilator chosen followed previously used ventilators. It was selected by some of the experts in the field. In addition, one could argue that the study may have saved a lot of lives because it was done before the widespread use of high-frequency oscillatory ventilation.

Hazinski: Av (Fanaroff), I thought the point you were going to make was that despite the power of that multicenter trial, it has failed to convince manufacturers not to build them and hospitals not to buy them. As people who have responsibility for training others, I'm sure we teach that the gold standard of clinical research is to perform randomized trials. And, yet, some people do not seem to be convinced by it. That's my comment.

My question to you Wally (Carlo) is: I like your illustration of the seesaw, but clinicians have to decide when to use or not to use this thing. So I want to ask you, are you using jet ventilation on patients that you think are not hopeless?

Carlo: Yes, we do. We would rather use it more for research. But in the meantime while we have to do research, we get clinicians who ask us to use it with their patients. Patients who are dying with severe hypercapnia tend to have resolution of hypercapnia soon after high-frequency jet ventilation is begun. Patients on very high pressures who may have reduced cardiac output may improve. Patients with bronchopleural fistula may also improve. Those are our usual indications. We have used it for PIE (pulmonary interstitial emphysema), but we are not convinced of what to do with PIE, although the randomized multicenter trial of jet ventilation in these patients revealed positive results.

Hazinski: Tennessee is real close to Alabama. I'm just wondering what we will have to do now that ...

Koff: Could I jump in here for a minute? One thing that strikes me about all the studies with high-frequency ventilation is that most of them were completed before surfactant administration had really come into play. Alan (Jobe), will you comment on the relationship between surfactant and BPD outcome? Do you think that surfactant will be one of the factors that is controlled in continued studies of high-frequency ventilation?

Jobe: Most babies with RDS will probably improve enough with surfactant treatments so that nonconventional ventilation techniques will not be needed. However, we will be left with a number of babies with other problems such as pulmonary hypoplasia, meconium aspiration, pneumonia, and pulmonary hypertension with respiratory failure. Some of these infants may respond to surfactant such that experimental ventilatory techniques and ECMO can be avoided.[1] Surfactant treatments should decrease the number of infants requiring special treatments for respiratory failure.

1. Auten RL, Notter RH, Kendig JW, Davis JM, Shapiro DL. Surfactant treatment of full-term newborns with respiratory failure. Pediatrics 1991;87:101-107.

Carlo: There's a multicenter trial being designed that will look at whether surfactant will help in combination with jet ventilation.

O'Rourke: Most of your cases have been neonates; even in this relatively homogeneous group of patients, the indications for HFV are uncertain. As HFV enters the armamentarium for pediatric patients (non-neonates), don't you agree that there will be even more difficult questions? This older group of patients are more varied in terms of age and etiology of disease.

Carlo: Yes, I think that's a very important observation, particularly when patients now come in so many different sizes. Pulmonary mechanics are really affected by patient size and disease.

Green: Wally (Carlo), would you comment on mucociliary clearance during high-frequency ventilation? Several years ago it was thought that mucociliary clearance might actually be enhanced by high-frequency ventilation, and yet you alluded to problems with blocking of ET tubes because of poor humidification. I'd like more data.

Carlo: There were a lot of preliminary papers or abstracts published 8 or 10 years ago. Not much has come out of that. I will say that the problem of airway obstruction seems to be secondary to poor humidification and temperature of the gas being used.

Therapeutic Approaches to the Infant with Bronchopulmonary Dysplasia

Ronald N Goldberg MD and Eduardo Bancalari MD

Introduction

The management of bronchopulmonary dysplasia (BPD) is fraught with problems—chief among them the maintenance of adequate gas exchange while avoiding progressive pulmonary damage. Therapies aimed at maintaining gas exchange, such as oxygen administration and mechanical ventilation, must be applied carefully because they are associated with important complications.

This paper examines the risks and benefits associated with therapies commonly used to treat infants with BPD. However, one must understand that therapies used to treat and support infants with respiratory failure may aggravate BPD. A general consideration of therapies used to treat infants with BPD must include efforts to attenuate the damaging effects of these supportive measures (ie, mechanical ventilation and oxygen administration).

Mechanical Ventilation

It is essential to limit as much as possible the duration and intensity of mechanical ventilation and supplemental oxygen exposure in infants at risk for BPD because these therapies are believed to be key factors in the pathogenesis of this disease.[1,2] Although expeditious weaning of these patients from mechanical ventilation is of primary importance, a gradual weaning approach often must be employed to prevent respiratory deterioration manifested by hypoxemia and hypercapnia. The lowest peak inspiratory pressures and respiratory rates necessary to maintain acceptable arterial oxygen (P_{aO_2}) and carbon dioxide (P_{aCO_2}) tension levels should be employed. To prevent further unevenness in the distribution of inspired gas, short inspiratory times and high peak inspiratory flows should be avoided. The duration of expiration must also be long enough to allow complete exhalation and to reduce the possibility of gas trapping. The application of low-level, positive end-expiratory pressure (PEEP) of 2-4 cm H_2O [0.2-0.4 kPa] may prevent alveolar collapse and reduce airway resistance (R_{aw}) by distending small airways.

Ventilatory assistance can be gradually reduced (depending on the amount of spontaneous respiratory effort present), thereby allowing the infant to perform an increasing amount of the respiratory work. The P_{aCO_2} may be allowed to increase to values in the 50s or 60s as long as the pH is within acceptable limits. In infants with poor respiratory effort, the use of respiratory stimulants such as aminophylline or caffeine may also facilitate weaning from the ventilator. These drugs are especially useful in very small preterm infants who make weak respiratory efforts and demonstrate frequent apnea.[3] When the patient is able to maintain acceptable blood gas values at low ventilator rates (< 15 breaths/min), extubation may be attempted.

Anything that may depress ventilation (such as drugs, metabolic alkalosis, or hypoxemia) should

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be avoided during the period of weaning. In very small infants, it is common to observe a loss of lung gas volume after extubation due to poor respiratory effort and weak chest-wall musculature. In some of these infants, the use of nasal continuous positive airway pressure (CPAP) during the first few hours or days following extubation may help to maintain lung gas volume and improve the chances for successful extubation.[4] This may also be helpful in infants with BPD when extubation is contemplated.

Oxygen Therapy

Although supplemental oxygen is the mainstay of therapy for infants with BPD, the adverse effects of breathing oxygen have been well demonstrated in animal models and include:[5,6] (1) increased exchange of fluid and macromolecules across alveolar and airway epithelium, eventually resulting in pulmonary edema, and (2) impairment of endothelial function and pulmonary fibrosis. The threshold fractional-inspired-oxygen concentration (F_{IO_2}) for oxygen toxicity in humans is unknown; however, it is reasonable to assume that an $F_{IO_2} > 0.21$ may have an adverse effect on the lungs. In a study by Griffith and co-workers,[7] normal adult patients were exposed to F_{IO_2}s believed to be clinically safe (0.21, 0.30, 0.40, and 0.50) for approximately 45 hours. This study demonstrated that F_{IO_2}s of 0.30 to 0.50 resulted in a dose-dependent increase in permeability of lung epithelium. It therefore seems reasonable to assume that ongoing toxicity may be minimized by maintaining the infant with respiratory distress syndrome (RDS) or resolving BPD on the lowest F_{IO_2} required to maintain reasonable oxygenation.

The level of P_{aO_2} that should be maintained to ensure relative physiologic normality while minimizing the likelihood of oxygen toxicity is not clear. Halliday et al[8] studied the effects of minor changes in F_{IO_2} in preterm infants with severe BPD. They noted that $P_{aO_2} < 55$ torr [7.3 kPa] correlated with both increased pulmonary vascular resistance and pulmonary artery pressure. Infants with BPD have pulmonary hypertension and increased pulmonary vascular resistance, which may be aggravated by increasing hypoxemia. Therefore, maintaining an adequate P_{aO_2} may not only avert hypoxemia but may also avert pulmonary hypertension and cor pulmonale.[9] Oxygen therapy reduces pulmonary artery pressure without significant respiratory depression in infants with chronic lung disease.[9,10] For these reasons, efforts should be made to keep the P_{aO_2} in the range of 55 to 65 torr [7.3 to 8.6 kPa]. It has been demonstrated that infants with BPD grow faster when adequate oxygenation is maintained through the use of supplemental oxygen than when oxygen is not administered.[11,12]

Diuretic Therapy

Diuretics are commonly used to treat pulmonary interstitial edema, which is an important pathologic finding of BPD. Most infants who develop chronic lung disease have had clinical evidence of a patent ductus arteriosus (PDA),[13,14] which may contribute to pulmonary edema. In addition, investigators have noted a greater intake of fluid in the first few days of life in infants who subsequently develop BPD compared to infants who do not develop BPD.[13,15] It has also been shown[16] that the increases in pulmonary blood flow and interstitial fluid secondary to PDA may result in decreased pulmonary compliance and increased R_{aw}. This may result in employment of more intense levels of ventilator and oxygen support, which may contribute to pulmonary damage and edema. This further aggravates the cycle because increased lung water may prolong the time the infant remains on assisted ventilation.[17-20]

Infants with BPD develop interstitial pulmonary edema irrespective of whether they develop a PDA. Their ability to tolerate normal fluid requirements appears to be compromised. These infants may have increased capillary permeability, secondary to oxygen toxicity and infection. Oncotic pressure tends to be low in these children because of the difficulty encountered clinically in delivering adequate calories while keeping fluid intake low. In part, this predisposition to edema may be related to the increase in antidiuretic hormone that has been noted in these infants.[21,22] Infants with severe obstructive airway disease may also have increased venous return and left ventricular dysfunction.[23] Lymphatic drainage also may be impaired by

interstitial edema and increased central venous pressure. The resulting pulmonary fluid accumulation produces more deterioration of lung function and may result in increased requirements for oxygen and ventilatory support.

Furosemide has been used extensively in infants with chronic lung disease to decrease pulmonary interstitial edema. This drug decreases pulmonary transvascular fluid filtration and reduces elevated pulmonary vascular resistance. Aside from its diuretic effect, furosemide exerts a systemic vasodilatory action. Furosemide reduces right ventricular preload by causing systemic dilatation and reducing pulmonary vascular pressure and fluid filtration.[24] Both can decrease extravascular water, which in turn can increase lung compliance.

The use of diuretics in infants with BPD has been shown to improve lung function.[25-27] Kao et al[26] observed that in infants with BPD, furosemide acutely decreased R_{aw} and increased specific airway conductance (sG_{aw}) and dynamic pulmonary compliance (C_{dyn}). Others[27] observed that furosemide given to premature infants recovering from RDS significantly increased lung compliance and decreased the alveolar-arterial oxygen-tension gradient [$P_{(A-a)O_2}$]. However, this improvement in lung function was not secondary to diuresis—suggesting that furosemide has a direct pulmonary effect.[27]

In a double-blind study, McCann et al[28] observed a decrease in ventilator and oxygen requirements in infants with BPD who were treated with furosemide. Minute ventilation ($\dot{V}_E$), alveolar ventilation, and C_{dyn} increased and venous admixture decreased. Their findings suggest that in infants with BPD furosemide may significantly improve lung function and enable earlier weaning from the ventilator and from supplemental oxygen.

Side Effects of Diuretic Therapy

Although diuretic usage may rarely lead to excessive water loss and dehydration, more commonly it results in urinary loss of electrolytes and hyponatremia, hypokalemia, and hypochloremia. A predictable result of chronic diuretic therapy is hypochloremic, metabolic alkalosis. Infants receiving diuretics on a long-term basis should be given a potassium-chloride supplement. Also commonly associated with diuretic therapy is hypercalciuria, which may result in nephrocalcinosis[29] and secondary hyperparathyroidism.[30] Investigators have noted renal calcifications on abdominal roentgenograms after as little as 12 days of therapy in preterm infants receiving furosemide at a dose of 2 $mg \cdot kg^{-1} \cdot d^{-1}$. Infants with renal calculi had calcium excretion rates of 10 to 20 times that of normal age-matched preterm infants. Hypercalciuria may also aggravate the development of rickets.[31] Sensorineural hearing loss[32] has also been attributed to furosemide usage.

Bronchodilator Therapy

The effectiveness of bronchodilator drugs in infants with BPD has been clearly established. Gomez-Del Rio et al[33] evaluated the effect of the $beta_2$-agonist isoetharine on the pulmonary function of neonates who demonstrated high R_{aw} after being exposed to mechanical ventilation but who did not exhibit evidence that chronic lung disease was present. After treatment with isoetharine, R_{aw} decreased significantly, C_{dyn} improved, but no significant change in heart rate was observed. These data suggest that infants with increased R_{aw} early in their disease will respond to bronchodilator therapy; however, the significant postbronchodilator decrease in R_{aw} observed in these infants lasted for only 30 to 40 minutes.

Kao and co-workers[34] evaluated the effect of isoproterenol inhalation on R_{aw} in infants with BPD. Pulmonary function was measured before and up to 6 hours after administration of the aerosol. These investigators noted that R_{aw} decreased approximately 28% and sG_{aw} increased 53%. The significant postbronchodilator decrease in R_{aw} lasted for only 30 minutes. Thoracic gas volume (TGV) and C_{dyn} did not change.

Sosulski et al[35] evaluated another $beta_2$-agonist, terbutaline sulfate, in mechanically ventilated infants with BPD. These investigators noted a significant improvement in C_{dyn} and R_{aw}, at 30 minutes, which lasted at least 60 minutes. Clinical improvement was manifested by decreases in P_{aCO_2} and wheezing. Rotschild et al[36] recently observed an increase in static compliance (C_{st}) and a decrease

in P_{aCO_2} after administration of salbutamol (albuterol). Furthermore, Brundage et al[37] combined salbutamol with the muscarinic antagonist ipratropium bromide and were able to decrease R_{aw} and increase lung compliance maximally for 2 hours, with some beneficial effect measured up to 4 hours after treatment.

Another potential benefit of $beta_2$-agonist aerosol therapy is its effect on mucociliary function.[38,39] Airway cilia beat and generate a wave of force that moves the airway mucus blanket towards the pharynx. High F_{IO_2}s depress and disrupt mucociliary transport. Laurenzi et al[40] showed in animal studies that mucus flow in the airway was increased by nebulization of racemic epinephrine or isoproterenol.

Use of bronchodilators in the newborn has been controversial because of the small amount of smooth muscle found in the airways of newborn infants. However, lung histology in infants with BPD demonstrates a significant increase in peribronchial smooth muscle.[41-43] This increase is at least partly responsible for the elevated R_{aw} documented in infants with BPD. Additional factors that may also be important in increasing R_{aw} are peribronchial swelling due to pulmonary edema and impaired clearing of secretions.

These studies suggest that infants may respond to bronchodilators during the early stages of BPD. It is possible that the high R_{aw} found early in infants who later develop chronic lung disease may also be a contributing factor to the development of lung damage.[44] By reducing R_{aw} and work of breathing, it may be possible to decrease the intensity and duration of mechanical ventilation. A lower R_{aw} will permit ventilation with lower transpulmonary pressures, reducing the risk of barotrauma. This may also improve the distribution of the inspired gas, thereby reducing the need for high inspired oxygen concentrations.

Use of Respiratory Stimulants

Methylxanthines, specifically aminophylline, have been used to facilitate weaning premature infants from assisted ventilation and to minimize infant exposure to the dangers inherent in mechanical ventilation.[3] In addition to bronchodilation, methylxanthines have been used because of their theoretical ability to improve diaphragmatic strength and decrease muscle fatigue.[45]

Harris and co-workers[3] evaluated the use of aminophylline to wean infants from mechanical ventilation. They showed that significantly more infants were successfully extubated within 72 hours of initiating aminophylline than were control infants. Significant decreases in P_{aCO_2} and increases in $\dot{V}_E$ were observed after aminophylline was administered. These data suggest that aminophylline facilitates weaning of low-birthweight infants from mechanical ventilation during the recovery phase of RDS. Inherent in these findings is the potential for this therapy to decrease the incidence of BPD. The improved ventilatory response to CO_2 seen in this study suggests that aminophylline stimulates central-nervous-system chemoreceptors.

Theophylline also has been studied in infants with BPD in an effort to evaluate its bronchodilatory action and effect on pulmonary function. It is postulated that many of the complications accompanying BPD, such as recurrent atelectasis and difficulty weaning from mechanical ventilation, are related either to increased R_{aw} or to an inability to maintain lung volume.

Kao et al[45] observed that administration of theophylline to infants with BPD resulted in a decrease in R_{aw} and an increase in lung compliance. These effects were enhanced by the addition of diuretics.[45]

It must, however, be remembered that methylxanthines have many side effects (eg, tachycardia, gastrointestinal irritation, and increased oxygen consumption)[46] and should be used with caution.

Steroid Therapy

The use of steroids to treat BPD was first reported in 1978 by Kramer et al.[47] Their original work was corroborated by a number of studies;[48-53] however, because of methodologic problems and low patient numbers, these early studies did not definitively affirm steroid therapy as the standard of care for BPD patients.

Potential mechanisms suggested to explain the beneficial effect of steroids in BPD include

stabilization of cell and lysosomal membranes, increased surfactant synthesis, inhibition of prostaglandin and leukotriene synthesis, decreased polymorphonuclear cell infiltration into the lungs, enhancement of beta-adrenergic activity, and diuretic activity.[54-56]

Avery et al[57] evaluated infants who were < 1500 g, 2-to-6-weeks old, and still required mechanical ventilation. The steroid group received steroids for 6 weeks and was weaned from mechanical ventilation more rapidly than the control group. Furthermore, infants in the steroid group were noted to have increased pulmonary compliance compared to those in the control group.

These findings were confirmed in a study by Cummings and co-workers[58] who compared a placebo group with two groups dosed with steroids for either 18 or 42 days. Study-entry criteria included a birthweight of ≤ 1250 g, and oxygen and ventilator dependence. More impressive improvement in outcome was observed in the 42-day steroid group. This group was weaned from supplemental oxygen and mechanical ventilation more quickly than either the control or 18-day steroid group. In addition, survival and neurologic outcome were improved in the 42-day steroid group compared to the other groups.

One must remember when interpreting these data that for the results of studies with small numbers to be valid we assume that the patients are similar in most respects except for the variable studied.[59] This is unlikely to occur in studies of human disease; therefore, large multicenter studies are needed.

Furthermore, important unanswered questions remain, such as optimal dose and frequency, eligibility, timing of steroid use, and side effects (eg, hypertension, hyperglycemia, and increased rate of infection).[46] Alkalay et al[60] evaluated adrenal function in 10 low-birthweight infants with BPD who were receiving dexamethasone. Five of these infants had suppressed adrenal function and required prolonged steroid treatment. These data suggest that dexamethasone therapy given for several weeks may be associated with prolonged suppression of the hypothalamic-pituitary-adrenal axis function in a substantial number of infants.

Vitamin-A Supplementation

Vitamin A influences growth and differentiation of epithelial cells. Induced deficiency of vitamin A results initially in basal-cell-layer proliferation of the epithelium of the conducting airways, followed by necrosis of columnar ciliated and nonciliated lining cells. These cells subsequently slough into the airway lumen as basal cells, become confluent, and differentiate into an atypical squamous layer. In addition, this results in abnormalities of mucociliary function and water transport across the trachea.[61,62]

A sufficient amount of vitamin A must be present for re-epithelialization to occur after airway damage. It has been postulated that if vitamin-A deficiency exists when injury occurs, squamous metaplasia will result, and normal healing will not occur.[63] In fact, the sequence of cellular changes mentioned above is similar to that seen in children with BPD.

Because of delivery at an early gestational age, very-low-birthweight neonates are deprived of much of the transplacental vitamin A that they would normally receive; therefore, they are born with limited hepatic stores of vitamin A and low plasma concentrations of vitamin A and retinol-binding protein. Furthermore, this deficiency is often prolonged because difficulties in establishing enteral feedings are commonly encountered.[63]

Shenai and co-workers[64,65] observed an increased prevalence of low plasma levels of vitamin A in infants with BPD compared to preterm infants without BPD. Levels were particularly low at 3-to-5-weeks postnatal age.

Shenai et al[63] initiated a clinical trial to test whether vitamin-A supplementation during early postnatal life could reduce the morbidity associated with BPD in infants who were oxygen dependent and who required mechanical ventilation for at least 72 hours after birth. BPD was diagnosed in 9 of 20 infants receiving vitamin-A supplementation and in 17 of 20 control infants. The need for supplemental oxygen, mechanical ventilation, and intensive care was reduced in infants receiving vitamin-A supplementation compared to controls. While these data are encouraging, this hypothesis must be tested in more extensive trials before it can be generally accepted.

Conclusion

This brief review has focused on current therapies used in the treatment of BPD. What must be stressed is that each infant needs to be approached individually with therapies tailored to his or her particular disease state. Once initiated, therapies must be continually evaluated to minimize side effects and risks.

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Abbreviations Used in this Paper

BPD	— Bronchopulmonary dysplasia
C_{dyn}	— Dynamic lung compliance
CPAP	— Continuous positive airway pressure
C_{st}	— Static lung compliance
F_{IO_2}	— Fractional inspired oxygen concentration
P_{aCO_2}	— Arterial carbon dioxide tension (pressure)
P_{aO_2}	— Arterial oxygen tension
PDA	— Patent ductus arteriosus
PEEP	— Postitive end-expiratory pressure
R_{aw}	— Airway resistance
RDS	— Respiratory distress syndrome
sG_{aw}	— Specific airway conductance
TGV	— Thoracic gas volume
$\dot{V}_E$	— Minute ventilation

Goldberg Discussion

Orenstein: Ron, I enjoyed that! What about the nonsteroidal anti-inflammatory agents? A few years ago Kurt Stenmark presented a paper showing beneficial effects from cromolyn sodium in a group of infants with BPD. I don't think he's published that work yet, other than the original abstract.[1]

1. Stenmark KR, Eyzaguirre M, Remigio L, Secombe J, Henson PM. Recovery of platelet activating factor and leukotrienes from infants with severe BPD: Clinical improvement with cromolyn treatment (abstract). Am Rev Respir Dis 1985;131:A236.

Goldberg: As far as I know, the only work I have seen is that work by Stenmark and co-workers[1] who noted an increase in eicosanoid production in the lung lavage fluid of infants with BPD. These investigators then went on to suggest that if you give a mast-cell-stabilizing substance such as cromolyn sodium, you can decrease the inflammatory response and actually can measure significant changes in pulmonary function. It is not clear to me whether steroids will ultimately be the best drug to use in BPD or if in fact their major effect is on inflammation. It is possible that the dramatic clinical effects seen with steroids have nothing to do with inflammation. It is possible that fluid shifts secondary to steroids may also be very important.[2]

1. Stenmark KR, Eyzaguirre M, Remigio L, Secombe J, Henson PM. Recovery of platelet activating factor and leukotrienes from infants with severe BPD: Clinical improvement with cromolyn treatment (abstract). Am Rev Respir Dis 1985;131:A236.
2. Torre J, Yeh TF, Anyebuno M, Rastriegi A, Pildes RS. Early dexamethasone therapy: Fluid and electrolyte balance and renal function in premature infants with RDS (abstract). Pediatr Res 1989;25:73A.

Jobe: All your models of inflammation involve the endothelium. Were the epithelial responses the same or different?

Goldberg: I believe that the response should basically be the same. There are alveolar macrophages that would react the same way as the intravascular macrophage (ie, release inflammatory mediators and leukotrienes).

Jobe: Could you comment on the use of vitamin A, given the provocative reports from Vanderbilt?[1,2]

1. Shenai J, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987;111:269-277.
2. Stahlman MT, Gray ME, Chytil F, Sundell H. Effect of retinol on fetal lamb tracheal epithelium, with and without epidermal growth factor. Lab Invest 1988;59:25-35.

Goldberg: That clinical trial from Vanderbilt University[1] suggests that supplementation of intravenous alimentation with vitamin A results in a decreased incidence of bronchopulmonary dysplasia. This is fairly exciting information. Part of the problem with neonatal care is delivery of adequate calories and micronutrients. Poor nutrition is probably a major causative factor in BPD.

1. Shenai J, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987;111:269-277.

Hazinski: I recommend that paper[1] for people to review in their journal clubs. I think it's a very carefully done small study. Its results, I think, have been misinterpreted, however, in that people have dismissed it by saying that the incidence of BPD in the control group was 90%. The reason is because the study was designed that way; the study population was intentionally enriched for the outcome of interest. The eligibility criteria were chosen to increase the chances that there would be high incidence of BPD. So, not every premature baby was admitted to the study—only ventilator babies who had reached some predetermined level of severity were admitted.

1. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987;111:269-277.

Goldberg: Could you comment on the delivery of vitamin A?

Hazinski: Vitamin A is photodegraded in an aqueous solution, so if you add it to the aqueous portion of hyperalimentation, some of it is degraded in several hours. If you put it in lipids, this might protect it from photodegradation, although I don't think that's been studied.

Jobe: And you have no BPD?

Hazinski: No! We have a lot of BPD because we have many babies less than 900 g who receive surfactant and survive, Alan!

Martin: I happen to like your emphasis on the inflammatory response.

Goldberg: I didn't emphasize this as much as I should have. Many of these mediators, such as leukotriene C4 and D4, thromboxane A2, and platelet-activating factor can cause bronchoconstriction.

Koff: You've been talking a lot about oxygen-related injuries. A few years ago Wung et al[1] reported that using higher CO_2 levels helped reduce the incidence of BPD. Could you comment on that?

1. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation without hyperventilation. Pediatrics 1985; 76:488-494.

Goldberg: I think that accepting higher P_{aCO_2} values means that people are using lower ventilator pressures, which may lessen the barotrauma associated with BPD.

Hazinski: Shirley Murphy[1] did a study on intubated babies with BPD, asking the question, "How much cromolyn gets into the lung of a mechanically ventilated baby." It's a very nice study. It was published in abstract form last year or the year before. She found that she could account for 99% of the administered cromolyn, either in the expiratory gas or in the baby's urine. If cromolyn is working, it must be very dependent on how much gets into the lung.

1. Wattenburg K, Clark A, Murphy S. Aerosolized cromolyn delivery to intubated babies (abstract). Pediatr Res 1988;23:570A.

Fanaroff: Ron (Goldberg), I enjoyed that very much. If I understand correctly, BPD is a very complex multiorgan-system disorder (there's heart, lung, immune system, endocrine system, with nutritional overlay). I've been impressed by the fact that we recognize it as undernutrition, but it's a resistant form of undernutrition, and it doesn't matter how many calories we throw on board or what mixture we try. Do you have any secrets on how we can correct the undernutrition?

Goldberg: No, I think we have the same difficulty everyone else has. I think that it might help if we gave lipids earlier to small preterm infants and possibly if we instituted early low-volume feedings.

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Note to publishers: Send review copies of books, films, tapes, and software to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593

Essentials of Pediatric Intensive Care, edited by Daniel L Levin MD and Frances C Morriss MD, with 138 contributors. Softcover, illustrated, 1,137 pages. St Louis: Quality Medical Publishing Inc, 1990. $49.95. To order call 314-878-7808 or 1-800-423-6865.

Whether the book **Essentials of Pediatric Intensive Care** lives up to its title may be open to debate. Its 1,000-plus pages of extensive narrative address a wide variety of topics in pediatric and neonatal care. Among these topics are some of the most common and important problems encountered by specialists in these fields. Also included are discussions of some of the more unusual and perhaps unlikely problems to be seen in the pediatric or neonatal ICUs. The authors, faculty members at the University of Texas Southwestern Medical Center, write from their experience at Children's Medical Center and Parkland Memorial Hospital in Dallas.

The 51 chapters that make up the text are arranged into 4 main sections. Part I, composed of 6 brief chapters collectively called "General Principles," offers information on the ICU routine: admitting the patient, organizing nursing care, and assessing and monitoring the patient. The chapter "Drug Monitoring and Pharmacokinetics" at this section's end is well written but seems misplaced here.

Part II is entitled "General Major System Failure." The apparent intent of this section is to focus upon general causes and effects of organ or system failure. Therefore, the reader might expect a half-dozen lengthy chapters covering the body's major systems. Instead, the section includes 19 brief chapters that vary greatly in their specificity. Respiratory failure and renal failure are each covered in a single chapter; whereas, no fewer than 5 chapters focus on neurologic dysfunction. For consistency these chapters could be compiled into a single, more comprehensive chapter. As in Part I, some chapters seem misplaced: The chapter on "Status Epilepticus" would seem to fit more properly in Part III ("Specific Diseases and Problems"), as would the chapter on anaphylaxis. I believe that Chapter 25, which focuses on management of donated organs, would be more appropriate in Part IV ("Equipment and Techniques").

Part III is arrranged by organ systems, which helps to make it easier for the reader to find some pieces of specific information. In addition, however, Part III includes substantial sections on anesthesia and surgery, poisonings, trauma, and infections, as well as psychological, social, legal, and ethical aspects of pediatric care. Thus, some chapters relevant to a given system may appear under other headings within this portion of the book. For example, "Aspiration Pneumonia" appears in the section labeled Trauma, instead of in the pulmonary section.

The final section of the book is dedicated to equipment and techniques of pediatric intensive care. Chapters in this section briefly discuss indications for use of particular equipment or procedures, their potential hazards, and general principles of operating pieces of equipment or performing specific procedures.

I found the most valuable information in this text to be in Parts III and IV. In general, Part III covers many of the most important problems commonly encountered in pediatric ICUs, and Part IV provides good explanations of many vital pieces of equipment and key procedures.

The sheer size and scope of this book is impressive. It is informative, interesting, and easy to read. Its organization is confused, though, and the book lacks the cohesiveness and emphasis on essentials that a book of this type needs. Perhaps this is a natural outcome of having 138 different contributors, but I feel the editors could have been more judicious in selecting and arranging the chapters. Instead of being a tightly knit volume containing only essential material, this text is more accurately an anthology of collected papers on pediatric intensive care. The editors have buried the essential material among many interesting but arguably nonessential topics, and have failed to distinguish between them.

Furthermore, although the editors state that the book is designed as a practical reference for physicians, nurses, respiratory care practitioners, and students, some clinicians will find it more useful than do others because the book is uneven in its coverage of problem areas. For example, respiratory problems are given generous coverage as the main focus of 8 or more chapters in Part III. By contrast, cardiac problems warrant just 3 chapters, and only 13 pages are dedicated to renal disease. An individual chapter is dedicated to injuries incurred by lightning, but closed head trauma is not mentioned anywhere in the book. Although the toxicology section contains a chapter on brown-recluse spider bites, overdoses of heroin, barbiturates, and alcohol merit only a few difficult-to-locate paragraphs within a chapter on "General Considerations of Poisoning."

Despite its inconsistencies and lack of balance, **Essentials of Pe-**

diatric Intensive Care is an appealing and unique book. Although the uninitiated reader may find it difficult to pick out the truly essential material, the experienced pediatric ICU clinician will find it fairly accessible. And, after putting the essential materal to use, the experienced practitioner may enjoy reading about lightning and spiders.

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An Introduction to Clinical Research, by Catherine DeAngelis MD MPH and APA Committee. Hardcover, illustrated, 166 pages. New York: Oxford University Press, 1990. $24.95.

The author, Catherine DeAngelis MD MPH, Professor and Deputy Chairman, Department of Pediatrics, The John Hopkins School of Medicine, states that the goal of this book is to serve as a primer for the novice researcher who wants to do clinical research. The manual was written by a committee of the Ambulatory Pediatric Association (APA) spearheaded by the author, a former APA president, who made the manual a special project during her term in office because one of the APA's goals is to encourage and enhance clinical research.

Although the manual is not meant to provide the reader with in-depth information on all aspects of clinical research design, the author claims that it is possible to conduct a simple, important clinical research project using the information contained in the text, with some guidance from an experienced clinical researcher. The Suggested Readings sections at the end of each chapter contain references to address the problems that are beyond the scope of the text. An annotated bibliography at the end of the book includes articles and texts that can assist the reader who wants to read more about performing clinical research.

Chapter 1 sets the stage for later topics by covering some of the key aspects of the scientific method, inference and validity. Four aspects of validity and the inferences that can be made to the larger world are discussed. The chapter author concludes that the value of research depends on the validity of the inferences that can be made from the study.

In Chapter 2, the authors discuss how to develop the research question and how to use hypotheses to determine the feasibility of the research project. This chapter includes a useful, albeit basic, discussion of how to identify dependent and independent variables from the research questions. The value of using a consultant to help determine how the data will be collected is also discussed, and the chapter ends with a description of how to use a personal computer to search 16 different data bases developed by the National Library of Congress—MEDLARS (Medical Literature Analysis and Retrieval System).

Chapter 3 deals with selecting study subjects, making decisions related to sample selections, and estimating appropriate sample size, and addresses the power of the sample, confidence intervals, and the impact of attrition of study subjects. Methods for assigning participants to the experimental and control group are also discussed.

In Chapter 4, "Research Models and Methods," the author describes and classifies different research study designs—the case series design, the case-control study, and the clinical trial—categorizing them by the way in which their subjects have been gathered and compared. This chapter outlines "rules" that apply broadly to nearly all designs. Attributes of studies are covered, with examples to illustrate prospective versus retrospective, descriptive versus comparative, observational versus experimental studies. General requirements for subject selection and observation are briefly discussed including criteria for inclusion in the observed group. The importance of identifying the available universe for eligible subjects, assessment of bias in the available universe of patients, and development and consistent application of rules for classifying observations are covered. The strengths and weaknesses of different types—comparative studies, case-control, observational cohort studies, and experimental studies—are discussed, with the key elements of each type of study clearly outlined. The kinds of studies suited to clinical trials are described, and examples are given. An annotated bibliography provides suggested readings that lead the reader to a more in-depth treatment of the topics covered.

Data collection, management, and analysis are covered in Chapter 5 including sections on deciding what to collect, how to collect, and how to determine the validity and reliability of the measure used to collect the data. Content (face) validity, criterion validity, and construct validity are explained, and examples are provided to illustrate how each type is assessed. Errors introduced by poor intra- and interrater reliability are explained and suggestions provided for establishing the degree of reliability. Data management procedures (use of procedure manuals, coding manuals, and data entry programs) are discussed. Data analysis is explained first by a concise but comprehensive review of the types of variables that can be used. A good introduction to terms (the differences between mean, median, and mode, and definitions of variance and standard deviation, with

the impact of outliers) is provided. This chapter also introduces the reader to several statistical tests of significance and provides examples of variables that can be compared with each test. The authors point out that "a well conducted and well analyzed research project is meaningless if no one ever hears about it," and make suggestions for writing an abstract, presenting the abstract, and publishing study results in a peer-reviewed journal.

Strategies for funding research studies are covered in Chapter 6 including projecting costs, mechanisms for minimizing costs, and funding sources. Tips for applying for research support are discussed with ideas provided for applying to both public and private funding sources.

Chapter 7 deals with the critical appraisal of research, providing separate discussion of etiology of disease, diagnosis, prognosis, therapy, and screening. The last chapter is an annotated bibliography of 33 texts that the reader can use to read more deeply into areas introduced by this book.

Dr Angelis in the preface states that this book should be "a primer for the novice researcher and is meant to stimulate clinicians to do clinical research." She and her colleagues on the APA committee have accomplished this goal by writing a well-organized and easily read text that introduces the reader to a wide array of clinical research topics. This text should be read by respiratory therapists interested in conducting a clinical research study *before* they begin collecting data. The advice presented by the authors should help clinicians do the planning necessary to produce a successful investigation of some of the unanswered questions confronting respiratory care practitioners. This book is a valuable resource for anyone interested in helping a novice researcher conduct a clinical study.

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The Essentials of Respiratory Care, 3rd ed, edited by Robert M Kacmarek PhD RRT, Craig W Mack MM RRT, and Steven Dimas RRT. Hardcover, 681 pages, illustrated. St Louis: Mosby-Year Book Inc, 1990. $46.95.

The goal of the book (written primarily to be used in preparation for registration, certification, and licensure examinations) is to "present the knowledge base required of respiratory care practitioners in a logical and concise manner." I applaud the editors for attaining that goal; I have also found the text to be helpful as a quick reference on all aspects of respiratory care.

The entire text is in outline form that begins with a review of the basic sciences and the anatomy and physiology of the respiratory, cardiovascular, renal, and nervous systems, and then proceeds in logical progression through the essential aspects of respiratory care. Each chapter contains a bibliography, which I found to be helpful; and the Table of Contents is also in outline form, which makes it easy to locate a particular subject of interest.

Compared to the second edition, coverage of neonatal and pediatric respiratory care has been expanded from 3 to 5 chapters. In addition, chapters are included on nutrition, pulmonary rehabilitation, respiratory home care, and high frequency ventilation. I am particularly impressed with the chapter on nutrition, which is thorough and easy to understand; the inclusion of this topic will help to broaden the respiratory care practitioner's perspective.

The illustrations are numerous and well done, enhancing the authors' ability to communicate the intended objectives of the subject matter.

Overall this text is a valuable resource that all respiratory care practitioners, respiratory care departments, and respiratory care programs should not be without. I commend the authors for their thoroughness in writing this text. The book is a bargain at $46.95.

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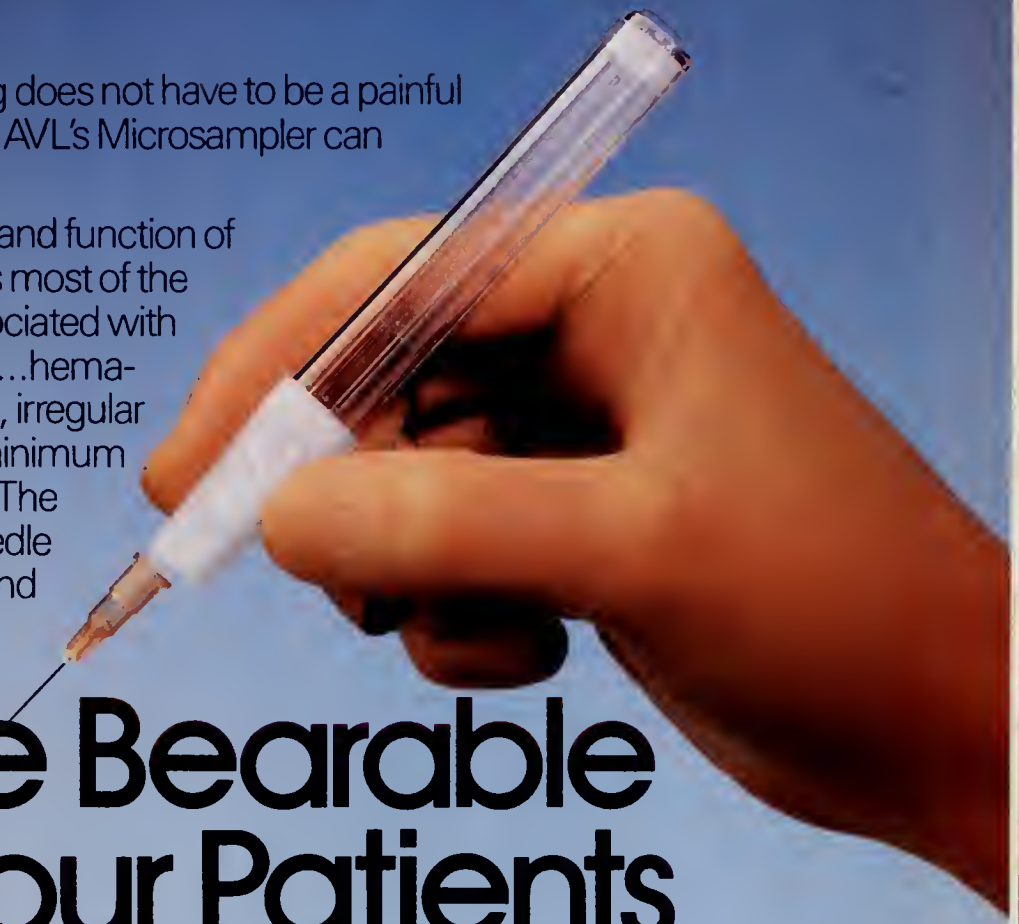

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Prevention of Spontaneous, Non-Manual Endotracheal Extubation

The use of soft endotracheal (ET) tubes and large-diameter low-pressure cuffs for prolonged ET intubation has decreased the risk of pressure necrosis of the trachea. At the same time, however, the increased mobility of modern ET tubes has led to the new problem of spontaneous, non-manual extubation (not to be confused with self-extubation by agitated, uncooperative patients). Ripoll et al[1] and Lindholm and Grenvik[2] have studied spontaneous extubation intensively and demonstrated, experimentally, that it is intensified when high positive end-expiratory pressure (PEEP) and high peak inspiratory pressure (PIP) are used.

Nasotracheal intubation alleviates this problem without sacrificing the advantages of soft low-pressure-cuffed tubes, but nasotracheal intubation is associated with an unacceptably high incidence of purulent nasal sinusitis in the critically ill patient.[3] Various tube-holder systems have been introduced but have not found clinical support,[4] and pre-shaped orotracheal tubes reinforced to resist bending forces, as suggested by Ripoll et al,[1] are not commercially available.

At our Level I trauma center, we experienced three to five spontaneous extubations monthly during 1989, when we had an average of 171 ventilation days/month in our ICU. Seeking to prevent the occurrence of these spontaneous extubations, we instituted a protocol based on the work of Ripoll et al[1] and Lindholm and Grenvik.[2] In this protocol we used the preshaped, stiff Berman oropharyngeal airway (Graham Field & Co, Hauppaug NY), taped to the orotracheal tube and then taped conjointly to the patient's face. This was intended to stent the endotracheal tube and prevent it from bending with each respiratory cycle and from moving with each patient-position change.

Experimentally, we used the Berman airway on all patients who required ET intubation and did not exhibit underlying peri- or intra-oral trauma, which would have precluded its safe placement. We began this protocol on December 19, 1989, and employed it on 34 patients until January 24, 1990. No spontaneous extubations occurred among these patients; whereas during the same period, spontaneous non-manual extubation did occur in 3 of 14 patients who did not have the Berman airway in place.

However, three of the Berman airway patients developed lip and tongue pressure ulcers from the presence of the oropharyngeal airway, which led us to discontinue the experiment and to stop use of this technique.

In the absence of a satisfactory method of stabilizing ET tubes, we recommend the monitoring of orally intubated patients as follows:

- Monitor placement and position of the ET tube on daily chest radiograph.
- Investigate cuff leaks because this may be a sign that the cuff is located at the vocal cords.
- Carefully tape the ET tube to the face, and carefully re-tape it when required.
- Record the tube level at the teeth daily.

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Steven E Ross MD
Department of Surgery
Division of Trauma
Cooper Hospital/
University Medical Center
University of Medicine and
Dentistry of New Jersey
Camden, New Jersey

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Reprints: Christina G Rehm MD, Division of Trauma, Three Cooper Plaza—Suite 411, Camden NJ 08103.

Validation of Control System for Ribavirin Aerosol

In the November 1990 issue of this journal,[1] my colleagues and I reported on the results of the application of engineering and administrative controls to contain aerosolized ribavirin. I present here the results of further

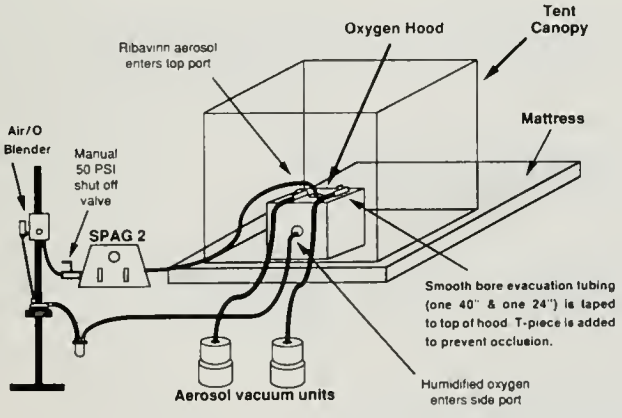
Table 1. Results of Personal and Area Sampling with Engineering and Administrative Controls in Force

Shift	No. of Break-ins	Total Caregiver Time in Tent (min)	Caregiver Time in Room (h)	Volume Collected (L)	Detectable Limit ($\mu g/m^3$)	PPE PF10	Result without PPE ($\mu g/m^3$)	Result with PPE ($\mu g/m^3$)
Personal sample 9 PM-6:30 AM (3-15-91)	8	125	9.5	1140	2.07	9970	4.05	0.4
Area sample (foot of bed) 9 PM-6:30 AM (3-15-91)	NA	NA	9.5	1140	2.07	NA	ND	NA
Personal sample 7:30 AM-3:30 PM (3-16-91)	13	185	8.0	960	2.46	Wilson HF	4.54	0.45
Personal sample 9 PM-6:30 AM (3-16-91)	3	68	9.0	1080	2.19	Wilson HF	ND	ND
Personal sample 7:30 AM-3:30 PM (3-17-91)	7	197	8.5	1020	2.31	Wilson HF	4.73	0.47

PPE = personal protective equipment.
PF = protection factor.
NA = not available.
ND = none detectable.
HF = half-face air purifier.

testing (Table 1). The reader is referred to our earlier paper for the details of the engineering and administrative controls imposed and the sampling equipment and analytical method employed, which were duplicated during the monitoring reported here.

The child under treatment while this sampling was done was 10 months of age, extremely active, and in an agitated state. Medical personnel from the Pediatrics service and the ICU decided to sedate him in order to contain him within the area of the


Tent Canopy
Oxygen Hood
Ribavirin aerosol enters top port
Mattress
Air/O Blender
Manual 50 PSI shut off valve
SPAG 2
Smooth bore evacuation tubing (one 40" & one 24") is taped to top of hood. T-piece is added to prevent occlusion.
Aerosol vacuum units
Humidified oxygen enters side port

PROTOCOL

(1) Use 2 aerosol vacuum units (Aerosol Delivery Hood Exhaust Units, ICN Pharmaceutical, Costa Mesa CA) or 370 mL/min of air volume to exhaust the tent.

(2) Before entering the oxygen hood or head tent, shut off nebulizer (SPAG unit) for 5 minutes by closing the automatic shutoff valve.

(3) Keep the tent canopy tucked under sheets on mattress of bed to help eliminate leakage.

Fig. 1. Double-containment system for ribavirin administration and protocol used in San Francisco General Hospital, San Francisco, California. (Adapted from Reference 1.)

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engineering control. With a more subdued child, results might have been even more favorable, but that is conjecture until additional monitoring has been done.

The area sample measurements shown in Table 1 indicate that for casual entry into the room, no personal protective equipment (PPE) is necessary if the engineering and administrative controls are being applied. It also indicates that no transmigration of aerosol to the corridor or adjacent areas occurs.

The personal samples reflect a slight excursion above the recommended 2.7 $\mu g/m^3$ (4.05, ND, 4.54, 4.73). The nondetectable result occurred during a period of fewer break-ins (3) and less caregiver time in tent (68 min) compared to periods of more break-ins and greater total caregiver time in tent (125, 185, and 197 min). With the PPE all results were well below the recommended standard of 2.7 $\mu g/m^3$ with a protection factor (PF) of 10×.

We conclude and recommend: (1) These results show the integrity of the engineering system in reducing levels of ribavirin aerosol to safe levels for those casually entering the room. Caregivers who must break into the tent should use a personal, fit-tested respirator with a 10-fold PF; (2) the child's activity may have affected the levels of ribavirin detected but this remains to be demonstrated; and (3) the engineering system should be used when ribavirin therapy is delivered.

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Environmental Health & Safety
San Francisco General Hospital
Medical Center
San Francisco, California

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Ventilator Circuits: What You See May Not Be What You Get

Knowledge of the function and limitations of equipment is one of the key attributes the respiratory care practitioner brings to the bedside. However, increasing sophistication in the intensive care unit may place undue emphasis on highly technical equipment. Less advanced equipment in routine use (particularly disposable items) may be perceived as less important and, therefore, subject to less stringent evaluation. We present such an example, involving a disposable ventilator circuit.

During routine testing with a lung model, we observed spurious volume and flow readings from a Hamilton Veolar Ventilator (Hamilton Medical, Reno NV). In this instance, flowrate was overestimated by approximately 30% and tidal volume by 20-25%. We immediately recalibrated the disposable, variable-orifice flowsensor according to the manufacturer's recommendation. Inaccurate readings persisted. A new flowsensor was removed from its package, calibrated, and placed in the ventilator circuit. No improvement was noted. Evaluation of internal calibration was performed by one of us (DT) trained in the procedure, and no problems were identified. During examination of the second flowsensor, one of us (DT) noticed that the Y-piece in the ventilator circuit (Marquest, Englewood CO) was unusual. On further inspection we found that instead of being a simple Y-piece, a rectangular opening 4.5 centimeters long and 1.0 centimeter wide connected the inspiratory and expiratory tubes to the patient connection (Fig. 1). Figure 2 shows the outward appearance of a conventional Y-piece (Hudson-RCI, Temecula CA) and the Marquest Y-piece. We speculated that this opening caused enough flow resistance and turbulence to effect flowsensor accuracy. We took two Y-pieces of each type shown in Figure 2 and measured the pressure drop across each, with and without the connecting elbow at 0.5, 1.0, 1.5, and 2.0 L/s using a Timeter RT-200 calibration analyzer (Timeter, Lancaster PA). Table 1 demonstrates these results. We then capped the patient port of the Y-piece and measured the pressure drop across the Y-piece from inspiratory-to-expiratory side. This was done to

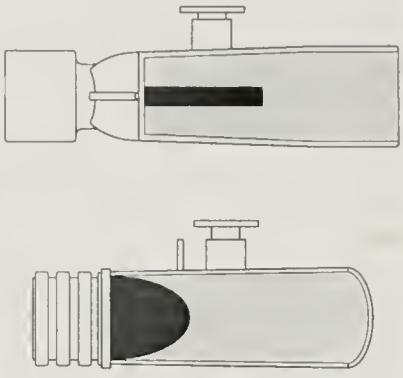

Fig. 1. The Marquest Y-piece (top) and a conventional Y-piece (bottom) in longitudinal section. The dark-shaded areas represent the path of gas flow to the patient. Note the rectangular opening in the Marquest Y-piece.

Fig. 2. External appearance of the Marquest Y-piece (left) and the conventional Y-piece, with connecting elbows.

Table 1. Average Pressure Drops across Y-Pieces with and without the Connecting Elbow

Flow	Pressure Drop (cmH_2O)			
	Hudson-RCI		Marquest	
(L/s)	Without	With	Without	With
0.5	0.5	0.18	0.13	0.28
1.0	0.31	0.69	0.53	1.08
1.5	0.51	1.46	1.29	2.37
2.0	0.96	2.61	2.25	4.40

simulate the use of continuous flow in the circuit, which is used clinically in the IMV, CPAP, and Flow-By modes of the Puritan-Bennett 7200a (Puritan Bennett Corp, Carlsbad CA). These results are shown in Table 2.

Table 2. Average Pressure Drops across Y-Pieces with the Patient Port Capped and Flow Traversing the Y from the Inspiratory to the Expiratory Side

Flow	Pressure Drop (cm H_2O)	
(L/s)	Hudson-RCI	Marquest
0.5	0.10	0.20
1.0	0.35	0.74
1.5	0.79	1.62
2.0	1.42	3.04

Tables 1 and 2 clearly show that pressure drop across the Marquest Y-piece is much greater than across the standard Y-piece in both situations. We are unaware of the rationale behind the change in Y-piece configuration in the Marquest circuit. Purchase of ventilator circuits in our institution is guided to a small extent by clinical use and evaluation and to a large part by competitive bidding by local manufacturers' representatives. To our chagrin, our evaluation (RB, RC) was obviously inadequate. To test our theory, we placed a 5-inch piece of flex tubing between the Y-piece and the flowsensor (Fig. 3). We hypothesized that this length of tubing would allow the flow to become less turbulent. Following this change, volume and flow readings were correct.

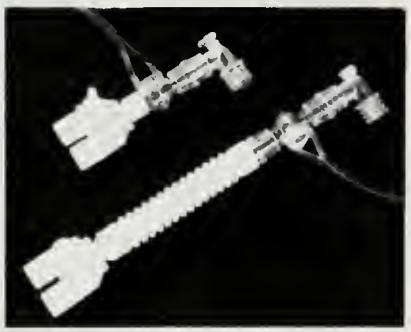

Fig. 3. Placement of the flowsensor directly above the Y-piece (its normal position) and at the end of the flex tube.

It is our contention that the Y-piece in question provides enough flow resistance to increase turbulence and prohibit proper flowsensor function. The effects this may have on other ventilators is unknown. However, we speculate that the increased resistance may add to imposed loads on the respiratory muscles, cause erroneous measurement of peak airway pressure, and interfere with other flow and volume measurement devices. Inaccurate measurement of airway pressure during spontaneous breathing from a demand valve or during flow by, may cause patient-ventilator dysynchrony. Certainly, in the case of a proximal airway flowsensor, function and accuracy are adversely effected.

Of note is the large change in pressure drop across the respective Y-pieces when the connecting elbow is added. Although some increase could be expected because of the 90° angle of the elbow, we were surprised by the magnitude of the increase.

We conclude that the Marquest Y-piece prevents proper function of the Hamilton Medical flowsensor due to increased turbulence created as gas traverses the rectangular openings. Consequently, we believe that this disposable ventilator circuit should not be used with either the Hamilton Veolar or Amadeus ventilators. In fact, we recommend that the manufacturer consider redesign of the Y-piece to a more conventional configuration. We also question the routine use of connecting elbows on ventilator circuits because of their effects on resistance. Perhaps a small, disposable flex tube that allows a more gradual angle of approach to the patient airway would be appropriate. Several manufacturers provide this type of connecting tube.

Lastly, we encourage practitioners to use the same scrutiny in evaluating the $2.00 components of the patient-ventilator system that they use in evaluating the $20,000 components.

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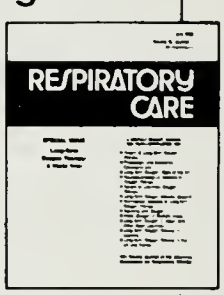

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June 12-14 in St Charles, Illinois. The ISRC presents its annual convention, "It's a Jungle Out There," to be held at Pheasant Run. Contact Trudy Watson RRT, Black Hawk College, 6600 34th Ave., Moline IL 61265. (309) 796-1311, ext 3303, or Vince Madama RRT, Rock Valley College, 3301 N Mulford Dr, Rockford IL 61103. (815) 654-4413 or (815) 654-4410.

June 27-29 in Monterey, California. The CSRC holds its 23rd Annual Meeting at the Doubletree Inn and Monterey Convention Center. Conference topics include "Liquid Perfluorchemical Ventilation," "DNAse Aerosol Therapy in Cystic Fibrosis," "Adult Exosurf," and Professor's Rounds, a 4-hour presentation featuring Neil MacIntyre MD, David Pierson MD, John Marini MD, and Robert Kacmarek PhD RRT. Contact John Bigler, Executive Director, CSRC, 24307 Magic Mountain Parkway #288, Valencia Ca 91355. To register call (800)-543-CSRC (2772).

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OTHER MEETINGS

June 11 in Chicago, Illinois. Christ Hospital and Medical Center hosts a seminar, "Respiratory Distress in the Newborn: Advances Beyond Conventional Ventilation," at the Holiday Inn-Chicago City Center. Sessions focus on maximum medical management, Exosurf therapy, jet ventilation in the management of respiratory distress, and ECMO. Contact Diane Ostrowski at (708) 857-1004, pager 2129.

June 17-July 26 in Mobile, Alabama. The University of South Alabama, Department of Respiratory Care and Cardiopulmonary Sciences conducts a 6-week nontraditional respiratory therapy program for registry eligibility. Contact William V Wojciechowski MS RRT, University of South Alabama, Department of Respiratory Care and Cardiopulmonary Sciences, 1504 Springhill Ave, Mobile AL 36604.

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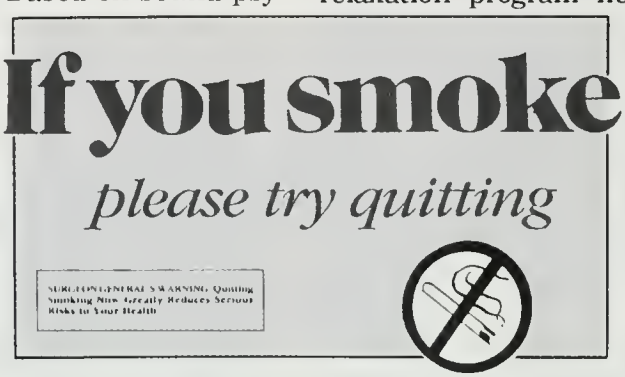

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Other tools for relieving anxiety after quitting and learning how to deal with irritability and other problems facing the new non-smoker are also a part of the *If You Smoke...* program. The 60-minute audio tape will take the participant through a progressive relaxation program helping the smoker relieve the new tension of quitting.

Health promotion and disease prevention is certainly one of your goals but you will also be able to fulfill important continuing education requirements by completing this two-session, six CEU course that will qualify you to conduct a smoking cessation program for your patients.

The program includes an instructor's manual, workbook, and companion audio tape and costs less than what an average smoker spends on cigarettes in five weeks.

Materials for your patients participating in the *If You Smoke...* smoking cessation program includes the workbook and 60-minute companion tape.

Item BK13-Instructor's Kit - includes manual, workbook, and 60-minute companion audio tape - $70 (AARC Members Pay Only $60)
Item BK14 - Participant's Kit - includes workbook and 60-minute companion audio tape - $28 (AARC Members Pay Only $18)

I want to help my patients quit smoking.
Send me:

_____ copy(ies) of *If you Smoke....* Instructor Kit—$70 (Members $60) BK13
_____ copy(ies) of *If you Smoke....* Participant Kit —$28 (Members $18) BK14

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RESPIRATORY CARE

Instructions for Authors and Typists

These Instructions are meant to guide authors and typists, including veterans in those roles, in the production of quality manuscripts. Perfection is not expected, but the well-prepared manuscript has the best chance for prompt review and early publication.

General Requirements

Submissions should (1) be related to respiratory care, (2) be planned for one of the publication categories below, and (3) be prepared as indicated in these Instructions. A letter accompanying the manuscript must specify the intended publication category, be signed by all the authors, and, when there are two or more authors, state that "We, the undersigned, have all participated in the work reported, read the accompanying manuscript, and approved its submission for publication."

Publication Categories

Research Article (Study): A report of an original investigation.
Evaluation of a Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification.
Case Report: A report of a clinical case that is uncommon or of exceptional teaching value. The author(s) must have been associated with the case. A case-managing physician must be one of the authors or, if not an author, must supply a letter approving the manuscript.
Case Series: Like a Case Report but including a number of cases.
Review Article: A comprehensive, critical review of the literature and state of the art of a pertinent topic that has been the subject of 40 or more published research papers.
Overview: A critical review of a pertinent topic about which not enough research has been published to merit a Review Article.
Update: A report of subsequent developments in a topic that has been critically reviewed (not necessarily in this journal).
Point of View: A paper expressing the author's personal opinions on a pertinent topic.
Special Article: If a paper does not fit one of the foregoing categories but is pertinent, the editors may consider it as a Special Article.
Editorial: A paper that draws attention to a pertinent concern.
Letter: A signed communication about material published in this journal or on topics of interest or value to readers.
Blood Gas Corner: A brief, instructive case report (real or fictional) involving invasively or noninvasively obtained respiratory care blood data, followed by questions for readers—with answers and discussion.
PFT Corner: Like Blood Gas Corner but involving pulmonary function testing.
Test Your Radiologic Skill: Like Blood Gas Corner and PFT Corner but involving pulmonary-medicine radiography and including one or two 4 × 5 or 5 × 7 inch prints of radiographs. The case must be real.
Review of Book, Film, Tape, or Software: Anyone interested in writing a review can discuss it with an editor.

Editorial Consultation and Author's & Typist's Kit

To discuss a writing project, write to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229 or call 214/243-2272.

Authors are urged to obtain the RESPIRATORY CARE Author's & Typist's Kit. The Kit provides *authors* with specific guidance about writing a research paper, writing a case report, converting to and from SI units, and in-house manuscript review. *Typists* can use the Kit's Model Manuscript, a list of journal name abbreviations, and a copy of these Instructions. The Kit is free from the Journal office.

Preparing the Manuscript

General Concerns—*Typist*

- Double-space ALL lines, including those in references, figure legends, and tables. Do not justify right margins.
- Number pages in upper right corner and leave margins of 1½" or more on all four sides of the page.
- For research articles, follow format of Model Manuscript, Respir Care 1984;29:182 (Feb 1984).
- Meticulously follow instructions for typing references.

General Concerns—*Author:*

- Structure manuscript as specified hereafter.
- Provide all requested information on title page as specified hereafter.
- Proofread manuscript for completeness, clarity, grammar, spelling; be sure all references, figures, and tables are cited in the text.
- Consider having paper reviewed in-house before submission.
- Have all co-authors proofread and approve manuscript and sign submission letter.

Manuscript Structure

Most kinds of papers have standard parts in a standard order. However, papers can vary individually, and not every paper will have all the parts listed here.

Research Article: Title page, abstract page, continuous text (Introduction, Materials & Methods, Results, Discussion), Product Sources page, Acknowledgments page, references, tables, figure legends. Please consult "Writing a Research Paper," Respir Care 1985;30:1057 (Dec 1985) and Model Manuscript, Respir Care 1984;29:182 (Feb 1984).
Evaluation of Device/Method/Technique: Title page, abstract page, continuous text (Introduction, Description of Device/Method/Technique, Methods of Evaluation, Results of Evaluation, Discussion), Product Sources page, Acknowledgments page, references, tables, figure legends.
Case Report or Case Series: Title page, abstract page, continuous text (Introduction, Case Summary, Discussion), Acknowledgments page, references, tables, figure legends. Also see "How To Write a Better Case Report," Respir Care 1982;27:29 (Jan 1982).
Review Article: Title page, Table of Contents page, continuous text (Introduction, History, Review of Literature, State of the Art, Discussion, Summary), references. May include figures & tables. No abstract. Table of Contents optional. Other formats may be appropriate.
Overview, Update, Point of View, or Special Article: Title page, text (introduction, message), references, tables, figure legends. No abstract.
Letter: Title page (provide a title), text, writer's name & affiliation, references. Tables & figures may be included. Double-space everything. Write "For Publication" on title page.

Structure: Important Details

Title Page: List title of paper, all authors' full names, degrees, credential letters, professional positions, and affiliations. List correspondence address, telephone number, and reprint address if desired. Name sources of grants or other support. Identify any author's consulting or commercial relationships that pertain to the paper's topic.

Abstract Page: Number this Page 1. List paper's title but omit authors' names. Abstract should be 200 words or less and must be informative, briefly specifying main points of paper, such as methods, results, and conclusions drawn.

Statistical Analysis: In research articles, identify statistical tests and chosen level of significance in the Methods section. In Results section, report actual P values.

Figures (illustrations): All photographs, diagrams, & graphs must be numbered as Figure 1, Figure 2, etc, according to the order in which each is first mentioned in the text. Photographs must be glossy prints 5 × 7 to 8 × 10 inches and should be black & white unless color is essential. Letters and numerals must be neat and large enough to remain legible if figure is reduced in size for publication. Final figures must be of professional quality, but 'rough' sketches may accompany the submitted manuscript, with final figures to be prepared after review. Identify each figure on back with a stick-on label showing figure number and arrow indicating top; omit author's name. Cover label with clear tape so ink will not smudge other prints. Supply three sets of unmounted figures. If figure has been published before, include copyright-holder's written permission to use it.

Figure Legends: List figure legends on a separate page, not on figures. If a figure has been published before, list the source in the legend.

Tables: Type each table on a separate page. Avoid more than 8 columns across. Continue a deep table on following pages. Give each table a number and descriptive title, placed above the table. Double-space ALL lines in tables, including column headings and footnotes.

Drugs: Brand names may be given, but always also show generic names.

Units of Measurement: In addition to conventional units of measure, show SI values and units in brackets after conventional expressions: ie, "PEEP, 10 cm H_2O [0.981 kPa]." For conversion to SI, see RESPIRATORY CARE 1988;33:861-873 (Oct 1988).

Commercial Products: If three or fewer commercial products are named in the text, list the manufacturer's name and location in parentheses the first time each is mentioned. If four or more products are named, do not list manufacturers in the text; instead, name the products and manufacturers in a Products Sources list at the end of the text. Provide model numbers when available.

Abbreviations: Use an abbreviation only if the term occurs several times in the paper. Write out the full term the first time it appears, followed by the abbreviation in parentheses. Thereafter, employ the abbreviation alone. Never use an abbreviation without defining it. Do not create new abbreviations unless absolutely necessary.

References:

- Use references to support statements of fact, indicate sources of information, or guide readers to further pertinent literature.
- Cite only published works—or works accepted for publication. When listing an accepted but still unpublished work, designate the accepting journal's name, followed by "(in press)."
- In the text, cite references by superscript numerals (half space above text), not in parentheses. The first reference cited in the text is number 1, the next is number 2, etc.
- In the reference list, place the cited works in numerical order.
- For the reference list, obtain author names, article and book titles, dates, volume and page numbers from the *original* cited articles and books, not from secondary sources such as other articles' reference lists, which often are inaccurate.
- Type references in medical-journal style. Examples appear at the end of these Instructions. Abbreviate journal names as in *Index Medicus*. A list of many journal-name abbreviations was published in Respir Care 1988;33:1050 (Nov 1988).
- DOUBLE-SPACE the lines of references.
- List ALL authors' names. Do not use "et al" to substitute for names.
- Identify abstracts, editorials, and letters as such. See examples.

Personal Communications, Unpublished Papers, and Unpublished Observations: List unpublished items in parentheses in the text, not in the reference list.

Examples of How To Type References

Notes: Although the examples here are printed with single-spaced lines, please double-space references in manuscripts. Also, note that words in article and book titles are not capitalized—except proper names.

Standard Journal Article:

1. Shepherd KE, Johnson DC. Bronchodilator testing: An analysis of paradoxical responses. Respir Care 1988;33:667-671.

Corporate Author Journal Article:

2. American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33:1044-1046.

Article in Journal Supplement:

(Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to allow retrieval.)

3. Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986;89(3, suppl):139s-143s.

Abstract in Journal:

(Abstracts are not strong references; when possible, full papers should be cited. When cited, abstracts should be identified as such.)

4. Lippard DL, Myers TF, Kahn SE. Accuracy of pulse oximetry in severely hypoxic infants (abstract). Respir Care 1988;33:886.

Editorial in Journal:

5. Rochester DF. Does respiratory muscle rest relieve fatigue or incipent fatigue? (editorial). Am Rev Respir Dis 1988;138:516-517.

Letter in Journal:

6. Smith DE, Herd D, Gazzard BG. Reversible bronchoconstriction with nebulised pentamidine (letter). Lancet 1988;2:905.

Personal Author Book:

7. Nunn JF. Applied respiratory physiology. New York: Appleton-Century-Crofts, 1969.

Note: To specify pages cited in a book, place a colon after the year and then list the page(s). Examples: 1969:85 (one page), 1963:85-95 (series of contiguous pages), 1963:85,95 (separated pages).

Corporate Author Book:

8. American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group, 1977.

Book with Editor, Compiler, or Chairman as 'Author':

9. Guenter CA, Welch MH, eds. Pulmonary medicine. Philadelphia: JB Lippincott, 1977.

Chapter in Book:

10. Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, eds. Pulmonary medicine. Philadelphia: JB Lippincott, 1977:171-223.

Submitting the Manuscript

After preparing the manuscript according to these Instructions, perform a final proofreading and check for accuracy and completeness. Then mail three copies of the manuscript and three sets of figures to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229 (or Federal Express to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229). Manuscript copy on IBM-compatible or Macintosh disks in addition to the requisite three hard copies will facilitate processing (Macintosh preferred). Enclose a letter as specified under **General Requirements** at the beginning of these Instructions. Do not submit material that has been published or is being considered elsewhere.

Author's Checklist

1. Is paper for a listed publication category?
2. Does cover letter meet specifications?
3. Is title page complete?
4. Are all pages double-spaced and numbered?
5. Are all references, figures, and tables cited in the text?
6. Are references typed in requested style?
7. Have SI values been provided?
8. Has all arithmetic been checked?
9. Has manuscript been proofread by all authors?

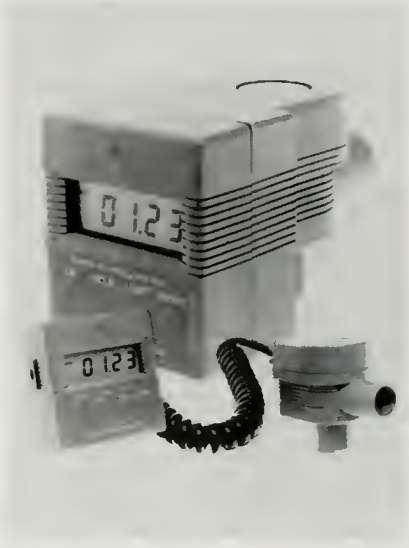
News releases about new products and services will be considered for publication in this section. There is no charge for these listings. Send descriptive release and glossy black and white photographs to RESPIRATORY CARE Journal, New Products and Services Dept, 11030 Ables Lane, Dallas TX 75229.

New Products & Services

RESPIRATORY MUSCLE TRAINER. According to the manufacturer, the Breather is the first and only patented respiratory muscle trainer designed to simultaneously train and strengthen both inspiratory and expiratory muscles. Resistance is provided during inhalation to strengthen the diaphragm and intercostal muscles, and during exhalation to strengthen the abdominal muscles. PAL Medical Inc, Dept RC, 235 S Maitland Ave, Suite 214, Maitland FL 32751. (800) 873-0773 or (407) 539-1304.

ROLLING WALKER. According to the manufacturer, the NextStep rolling walker is designed to provide walking assistance indoors and outdoors, and features large polyurethane wheels that glide easily over doorsills, carpeting, and uneven walkways while providing stability; easy-grip handbrakes; seat and tray attachments; big baskets for shopping; and the capability of carrying a portable ventilator. The NextStep is height-adjustable and folds for easy storage and transportation. With a maximum width of 22.5 inches and front wheels that extend 27.5 inches, the rolling walker is designed to be easily maneuvered through tight quarters and narrow doorways. NextStep walkers come in two models: the Standard with two handles, and the Crossbar for individuals with diminished strength in one hand. The Nextstep is imported from Sweden where it has been in use for 15 years. NobleMotion Inc, Dept RC, 2120 One Mellon Bank Center, Pittsburgh PA 15219. 1-800-234-9255.

PEAK FLOW METER. The Pocket Peak Flow Meter is designed for monitoring peak expiratory flowrate (PEF) in the hospital, clinic, physician's office, or patient's home. The unit features an operating mechanism consisting of a glass-reinforced epoxide-laminate vane that flexes to move a scale indicator; there are no springs or pistons to weaken or wear out. According to the manufacturer, the unit provides repeatability of ± 10 L/min at any reading on the 50-750 L/min graduated scale, and accuracy of ± 10% for readings under 400 L/min and up to ± 5% for a reading of 750 L/min. The Pocket Peak Flow Meter (supplied with a reusable plastic mouthpiece) is priced at $18.95 retail. The unit weighs 80 grams, and its overall size (without mouthpiece) is 5.5 × 4.5 × 1.25 inches. Ferraris Medical Inc, Dept RC, PO Box 344, 9681 Wagner Rd, Holland NY 14080. (716) 537-9151.



ELECTRONIC DIGITAL RESPIROMETER. The Electronic Digital Respirometer features a large easy-to-read LCD readout; a flow-sensing unit (with optional cable) that can be separated from the control unit for ease of patient use, cleaning, and mounting; durability (no gears, shafts, or bearings to break down); and a flame, acid, and alkali-resistant case. The 2-piece detachable respirometer comes with a 9-V battery and one 22-mm by 22-mm female adapter. Also available are spare flow-sensing units, 6-ft cable, AC adapter, and carrying case. Anesthesia Associates Inc, Dept RC, 460 Enterprise St, San Marcos CA 92069. (619) 744-6561.

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I. Type of Instn/Practice
1 ☐ Hosp. 500 or more beds
2 ☐ Hosp 300 to 500 beds
3 ☐ Hosp 200 to 300 beds
4 ☐ Hosp 100 to 200 beds
5 ☐ Hosp 100 or less beds
6 ☐ Clinic/Group Practice
7 ☐ Independent RT Provider
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II. Department
A ☐ Respiratory Ther
B ☐ Cardiopulmonary
C ☐ Anesthesia Service
D ☐ Emergency Dept

III. Specialty
1. ☐ Clinical Practice
2 ☐ Perinatal Pediatrics
3 ☐ Critical Care
4 ☐ Clinical Research
5 ☐ Pulmonary Func Lab
6 ☐ Home Care/Rehab
7 ☐ Education
8 ☐ Management

IV. Position
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C ☐ Supervisor
D ☐ Staff Technician
E ☐ Staff Therapist
F ☐ Educator
G ☐ Medical Director
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I. Type of Instn/Practice
1. ☐ Hosp 500 or more beds
2 ☐ Hosp 300 to 500 beds
3 ☐ Hosp 200 to 300 beds
4 ☐ Hosp 100 to 200 beds
5 ☐ Hosp 100 or less beds
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7 ☐ Independent RT Provider
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D ☐ Emergency Dept

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IV. Position
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C. ☐ Supervisor
D. ☐ Staff Technician
E. ☐ Staff Therapist
F ☐ Educator
G ☐ Medical Director
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Proventil®
(albuterol sulfate)
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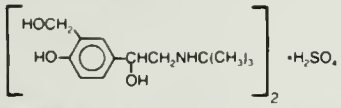
Unit Dose 0.083%*
0.5%* 20 mL bottle

*Potency expressed as albuterol

DESCRIPTION PROVENTIL, brand of albuterol sulfate, Solution for Inhalation, is a relatively selective beta$_2$-adrenergic bronchodilator (see **CLINICAL PHARMACOLOGY** section below). Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and the following chemical structure:



Albuterol sulfate has a molecular weight of 576.7 and the empirical formula $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The international generic name for albuterol base is salbutamol.

PROVENTIL Solution for Inhalation is available in two concentrations. The 0.5% solution is in concentrated form. Dilute 0.5 mL of the solution to 3 mL with normal saline solution prior to administration. The 0.083% solution requires no dilution prior to administration.

Each mL of PROVENTIL Solution for Inhalation (0.5%) contains 5 mg of albuterol (as 6.0 mg of albuterol sulfate) in an aqueous solution containing benzalkonium chloride, sulfuric acid is used to adjust the pH between 3 and 5. PROVENTIL Solution for Inhalation (0.5%) contains no sulfiting agents. It is supplied in 20 mL bottles.

Each mL of PROVENTIL Solution for Inhalation (0.083%) contains 0.83 mg of albuterol (as 1.0 mg of albuterol sulfate) in an isotonic aqueous solution containing sodium chloride and benzalkonium chloride, sulfuric acid is used to adjust the pH between 3 and 5. PROVENTIL Solution for Inhalation (0.083%) contains no sulfiting agents. It is supplied in 3 mL bottles for unit-dose dispensing.

PROVENTIL Solution for Inhalation is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that 10 to 50% of the beta receptors in the human heart may be beta$_2$ receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3.0 mg dose of nebulized albuterol, the maximum albuterol plasma level at 0.5 hour was 2.1 ng/mL (range 1.4 to 3.2 ng/mL). There was a significant dose-related response in FEV_1 and peak flow rate (PFR). It has been demonstrated that following oral administration of 4 mg albuterol, the elimination half-life was 5 to 6 hours.

Animal studies show that albuterol does not pass the blood-brain barrier. Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.

In repetitive dose studies, continued effectiveness was demonstrated throughout the 3-month period of treatment in some patients.

INDICATIONS AND USAGE PROVENTIL Solution for Inhalation is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS PROVENTIL Solution for Inhalation is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS As with other inhaled beta-adrenergic agonists, PROVENTIL Solution for Inhalation can produce paradoxical bronchospasm, which can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of sympathomimetic nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse. In individual patients, any beta$_2$-adrenergic agonist, including albuterol solution for inhalation, may have a clinically significant cardiac effect.

Immediate hypersensitivity reactions may occur after administration of albuterol as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

PRECAUTIONS General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, when given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of PROVENTIL Solution for Inhalation is unknown.

Information For Patients: The action of PROVENTIL Solution for Inhalation may last up to 6 hours and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking PROVENTIL Solution for Inhalation, other antiasthma medicines should not be used unless prescribed.

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat, at oral doses corresponding to 10, 50, and 250 times the maximum human nebulizer dose. In another study, this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects—Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given subcutaneously in doses corresponding to the human nebulization dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 0.1, 1, and 12.5 times the maximum human nebulization dose, respectively) showed cleft palate formation in 5 of 111 (4.5%) of fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) of fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) of fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) of fetuses at 50 mg/kg, corresponding to 250 times the maximum human nebulization dose.

Labor and Delivery: Oral albuterol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of PROVENTIL Solution for Inhalation is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of albuterol solution for inhalation in children below the age of 12 years have not been established.

ADVERSE REACTIONS The results of clinical trials with PROVENTIL Solution for Inhalation in 135 patients showed the following side effects which were considered probably or possibly drug related:

Central Nervous System tremors (20%), dizziness (7%), nervousness (4%), headache (3%), insomnia (1%).
Gastrointestinal nausea (4%), dyspepsia (1%).
Ear, Nose and Throat pharyngitis (<1%), nasal congestion (1%).
Cardiovascular tachycardia (1%), hypertension (1%).
Respiratory bronchospasm (8%), cough (4%), bronchitis (4%), wheezing (1%).

No clinically relevant laboratory abnormalities related to PROVENTIL Solution for Inhalation administration were determined in these studies.

In comparing the adverse reactions reported for patients treated with PROVENTIL Solution for Inhalation with those of patients treated with isoproterenol during clinical trials of 3 months, the following moderate to severe reactions, as judged by the investigators, were reported. This table does not include mild reactions.

Percent Incidence of Moderate To Severe Adverse Reactions

Reaction	Albuterol N = 65	Isoproterenol N = 65
Central Nervous System		
Tremors	10.7%	13.8%
Headache	3.1%	1.5%
Insomnia	3.1%	1.5%
Cardiovascular		
Hypertension	3.1%	3.1%
Arrhythmias	0%	3.0%
**Palpitation	0%	22.0%
Respiratory		
*Bronchospasm	15.4%	18%
Cough	3.1%	5%
Bronchitis	1.5%	5%
Wheeze	1.5%	1.5%
Sputum Increase	1.5%	1.5%
Dyspnea	1.5%	1.5%
Gastrointestinal		
Nausea	3.1%	0
Dyspepsia	1.5%	0
Systemic		
Malaise	1.5%	0

*In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

**The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

OVERDOSAGE Manifestations of overdosage may include anginal pain, hypertension, hypokalemia, and exaggeration of the pharmacological effects listed in **ADVERSE REACTIONS.**

The oral LD_{50} in rats and mice was greater than 2,000 mg/kg. The inhalational LD_{50} could not be determined.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL Solution for Inhalation.

DOSAGE AND ADMINISTRATION The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered 3 to 4 times daily by nebulization. More frequent administration or higher doses is not recommended. To administer 2.5 mg of albuterol, either dilute 0.5 mL of the 0.5% solution for inhalation to a total volume of 3 mL with normal saline solution, or administer the contents of one unit-dose bottle (3 mL of 0.083% nebulizer solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that the PROVENTIL Solution for Inhalation will be delivered over approximately 5 to 15 minutes.

The use of PROVENTIL Solution for Inhalation can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED PROVENTIL Solution for Inhalation, 0.5%, is a clear, colorless to light yellow solution, and is supplied in bottles of 20 mL (NDC-0085-0208-02) with accompanying calibrated dropper, boxes of one. **Store between 2° and 25°C (36° and 77°F).**

PROVENTIL Solution for Inhalation, 0.083%, is a clear, colorless to light yellow solution, and is supplied in unit-dose bottles of 3 mL each, boxes of 25 (NDC-0085-0209-01.) **Store between 2° and 25°C (36° and 77°F).**

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